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COUMADIN (WARFARIN) SODIUM*

A New Anticoagulant

JOSEPH H. NICHOLSON, M.D.,† AND THOMAS LEAVITT, JR., M.D.‡

LAWRENCE AND METHUEN, MASSACHUSETTS

THE introduction of bishydroxycoumarin (Dicumarol) about fifteen years ago evoked a voluminous literature on the use of anticoagulant treatment for the prevention and control of thrombotic and thromboembolic disorders. The early reports demonstrated that Dicumarol, by virtue of its depressing effect on the level or activity of plasma prothrombin, was an effective in vivo anticoagulant that could be usefully employed for the treatment of thrombosis and thromboembolism — particularly venous thrombosis and pulmonary embolism. These experiences also brought to light certain shortcomings of the drug.

A number of reports dealt with the prothrombin-depressing properties of congeners of the original Dicumarol. One cannot help being impressed with the diverse reports that possibly no single class of drugs has undergone closer scrutiny than the anticoagulants and that there is a real need for an anticoagulant agent with more ideal properties than those hitherto available. Despite the shortcomings of these drugs, it has been amply demonstrated that many thousands of lives have been saved and many more have been spared the ravages of thrombotic and thromboembolic complications by the use of the earlier anticoagulant drugs, notably Dicumarol.[1-3]

Although the introduction of Dicumarol in 1941 represented a major therapeutic advance, its limitations — particularly an unduly long latent period before its effect on the coagulation mechanism was manifested and an absence of predictability of effect from one patient to another or even in the same patient — were recognized soon after its introduction. Consequently, there has been a steady search by chemists for an anticoagulant that did not have the recognized limitations of the parent drug. This led in turn to the introduction into medicine of cyclocumarol (Cumopyran), ethyl biscoumacetate (Tromexan) and phenindione (Hedulin, Danilone) and others still in the investigative stage.

Experience has demonstrated that these compounds, in one respect or another, do not possess advantages over Dicumarol. Dicumarol, cyclocumarol and phenindione have long induction periods, and induced hypoprothrombinemia is not easily maintained. Tromexan has a relatively short induction period, but control of induced hypoprothrombinemia is most difficult of all. With all, and particularly with Tromexan, "escape" from a once-established therapeutic range is common. Thus, the objective of maintaining a steady and safe state of hypoprothrombinemia at a desired level is not readily obtainable. Phenindione, in contrast to the coumarin compounds, has given rise to serious toxic side reactions, other than hemorrhage.[4-8] Accordingly, there is a real need for a relatively safe anticoagulant that gives a rapid response and has a high predictability to induce and to maintain a relatively stable level of therapeutic hypoprothrombinemia.

Several suggested lists of requirements for an ideal anticoagulant have appeared. Goodman and Gilman[9] have proposed such a list. In their view, "Such an ideal drug would greatly extend the field of usefulness of anticoagulant therapy and thereby exert a salutary effect on the grave social and economic implications of thromboembolic disorders." Shapiro and Gordon[10] have extended the desiderata for an ideal anticoagulant.

For all practical purposes of anticoagulant therapy, such an ideal drug should meet the following criteria:

It should be active orally or parenterally.

It should have a good predictability of effect with the usual dose range for induction and maintenance of therapeutic hypoprothrombinemia.

It should induce an effective therapeutic hypoprothrombinemia soon after administration.

*From the Department of Medicine, Lawrence General Hospital, and the Bon Secours Hospital, Methuen.

†Assistant in medicine, Tufts University School of Medicine; senior staff member, Lawrence General and Bon Secours hospitals.

‡Assistant resident in obstetrics and gynecology, Boston Lying-in Hospital.

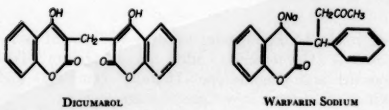
It should be easy to maintain the initially induced hypoprothrombinemia by subsequent relatively predictable doses.

It should produce a long period of hypoprothrombinemia initially, and, conversely, it should have a relatively short recovery period after administration of maintenance doses is discontinued.

It should have a low capacity to produce hemorrhage in the usual therapeutic dose range.

It should be readily counteracted, either if the prothrombin is depressed below the therapeutic range or if bleeding occurs.

It should have no systemic toxic effects.



DICUMAROL WARFARIN SODIUM

FIGURE 1. *Structural Relation of Dicumarol to Warfarin Sodium.*

Several reports on Coumadin Sodium suggest that this compound, developed in the laboratories of Dr. Karl Paul Link, where Dicumarol and cyclocumarol were discovered, meets the criteria listed above.[11] For this reason it was deemed worthy of clinical appraisal.

Coumadin Sodium is a monocoumarin compound, in contrast to Dicumarol, which is, as its name suggests, a dicoumarin compound. The relation is shown in Figure 1. In contrast to Dicumarol, cyclocumarol, Tromexan and phenindione, Coumadin forms a stable sodium compound. The sodium derivative is very soluble in water and it forms stable solutions that can be administered parenterally, as occasion may require. Its reported effectiveness by the oral, intravenous, intramuscular or rectal route may reside in this property. Elbe[12] reported that Coumadin Sodium diffused rapidly through the tissues of a rat when given intravenously. It was found in high concentrations in the plasma, muscle and liver five minutes after administration. In contrast to other synthetic anticoagulants, Coumadin Sodium passes promptly through the stomach wall after oral administration.

Shapiro[13,14] reported that 1 mg. of Coumadin Sodium per kilogram of body weight in man, administered intravenously or intramuscularly, induced a therapeutic hypoprothrombinemia (two to two and a half times the normal control in seconds) within twenty-four hours, that a plateau in the response curve generally lasted for about two or three days after the second day following the induction dose, that the hypoprothrombinemia could be reversed with vitamin K and that the drug had a predictable response pattern from patient to patient. Nichol[15,16] observed that it was easier to predict dosage with Coumadin than the other available anticoagulants and that, because of this, it might prove to be the safest of all coumarins. Shapiro did not use heparin in the 100 cases reported by him. Nichol pointed out that only two or three doses of heparin were needed because of its relatively prompt anticoagulant effect. Clatanoff and his associates[17] stated that the latent period and the time required to produce therapeutic hypoprothrombinemia are similar to those with ethyl biscoumacetate (Tromexan ethyl acetate), but the duration of action is more prolonged and it is less difficult to maintain a controlled stable level of hypoprothrombinemia; the latent period and time required to achieve therapeutic hypoprothrombinemia are shorter than those with either cyclocumarol or bishydroxycoumarin, whereas the duration of effect is similar. They also commented on the ease of restoration of excessive hypoprothrombinemia with vitamin K_1 — the periods of recovery ranged from four to twenty-four hours.

While our studies were under way, Pollock[18] reported on a three-year experience with the drug on 100 patients. His findings were essentially corroborative of the earlier reports and bore out the great predictability of response. Hypoprothrombinemia appeared at twenty-four hours, whether the drug was given intravenously or orally; phytonadione (vitamin K_1) in small doses (5 to 10 mg.) was an effective counteractant; the average maintenance dose was about 10 mg. per day and was consistent from day to day in the same patient. In Pollock's experience, Coumadin (warfarin) Sodium possesses properties that more nearly approach the ideal anticoagulant, because of early anticoagulant effect, smoothness of maintenance, lack of side effects and ease of restoration with vitamin K_1.

TABLE 1. *Thromboembolic Conditions for Which Coumadin Sodium Was Administered.*

CONDITION	NO. OF CASES
Acute myocardial infarction & intermediate coronary-artery disease	61
Pulmonary embolism	15
Thrombophlebitis (of lower extremities), acute	18
Arterial emboli	3
Cardiac disease*	3
Total	100

*Given by mouth prophylactically.

This review of the literature suggested that the drug might resolve many of the problems encountered in the management of anticoagulant therapy with the hitherto available anticoagulants. This is a report of our two-year experience, for acute thromboembolic episodes and prophylactic therapy on 100 patients in private practice and on the wards of the

Lawrence General and Bon Secours hospitals. As pointed out below, the results are in line with those previously reported.

Method and Material

Table 1 lists the thromboembolic conditions for which Coumadin Sodium was administered. The age distribution is shown in Table 2. Initial doses of 1 mg. per kilogram of body weight were usually given after a sample of blood was withdrawn for the first prothrombin determination; maintenance doses were administered by either an intermittent or a continuous dosage schedule. The size of the initial dose was chosen according to the patient's condition. The initial dose was lowered from the usual dose when the first prothrombin time indicated less than 100 per cent prothrombin, in patients who appeared to be frail or in the presence of signs of congestive heart failure. The distribution of doses in milligrams appears in Table 3.

Heparin was given for only about four doses in patients with pulmonary embolism, during the induction period.

Table 2. *Age Distribution of Patients Treated with Coumadin.*

Age	No. of Cases
yr.	
20-29	1
30-39	3
40-49	12
50-59	17
60-69	40
70-79	23
80 & over	4
Total	100

Originally, ampoules, 10 ml., or 75 mg. given intravenously, were used at the dosage indicated. When tablets* became available, we gave the drug orally, except in the presence of nausea or vomiting. Our early experience showed that there was no essential difference between the two modes of administration, as reported by Clatanoff et al.[17] and Pollock.[18]

The first maintenance dose was given as the prothrombin level rose from about 25 per cent. Subsequent maintenance doses were given either intermittently or by the continuous method. We attempted to achieve relatively constant levels within the therapeutic range. Although the drug is suitable for the intermittent method, our later trials showed that relatively constant levels of hypoprothrombinemia were more conveniently maintained by the continuous method with smaller doses given daily. Dosage was guided by daily estimation of prothrombin clotting times, the results of which were available at 10 a.m., the blood having been drawn two hours previously. We found that the maintenance dose was relatively constant for each patient. The first few doses provided a Coumadin "profile" from which subsequent doses could be readily estimated.

*This material was initially supplied by Dr. Samuel M. Gordon, director of research, Endo Laboratories, Incorporated, Richmond Hill, New York.

Table 3. *Distribution of Initial Doses of Coumadin.*

Dose	Patients Receiving Dose*			Totals
	group 1	group 2	group 3	
mg.				
37.5	—	4	2	6
40.0	—	—	1	1
50.0	6	12	7	25
55.0	—	1	—	1
56.25	—	2	2	4
60.0	2	1	3	6
62.5	7	17	5	29
65.0	1	1	—	2
68.0	1	—	1	2
70.0	1	2	—	3
75.0	4	8	8	20
81.25	1	—	—	1
Total				100

*Groups listed in Tables 4, 5 & 6.

Table 4. *Therapeutic Response to Initial Average Dose of 60 Mg.*

Group	Interval Required to Reach Therapeutic Range	No. of Patients	Dose	Interval Required to Obtain Therapeutic Effect	Peak Effect	Duration in Therapeutic Range
	hr.		mg.	hr.	days	days
1	24	23	61	22	3.1	3.4*
2	24-36	48	60	32	3.0	2.5
3	36-48	29	61.5	43	3.2	1.6

*3 omitted because of vitamin K.

A prothrombin level of 35 to 10 per cent was taken as the therapeutic range. This range was strictly adhered to. For example, if at twenty-four hours the value was recorded as 36 per cent but reached 32 per cent at the next twelve-hour determination, the patient was reported to have required between twenty-four and thirty-six hours to reach the therapeutic range. Clatanoff et al.[17] regarded 40 to 20 per cent as the therapeutic range. This difference may account for slight discrepancies between their study and ours.

Prothrombin estimations were made on whole plasma by the one-stage method of Quick,[19] using Simplastin as the source of thromboplastin. Control

TABLE 5. *Individual Response to Initial Dose.*

CASE NO.	INITIALS	AGE	DIAGNOSIS	INITIAL DOSE	THERAPEUTIC RANGE			
					INTERVAL REQUIRED	PEAK EFFECT	PROTHROMBIN	DURATION
		yr.		mg.	hr.	days	%	days
Group 1 (therapeutic range within 24 hr.):								
1	F.K.	75	Arterial embolus	68.0	24	3	12	5
2	J.B.	58	Myocardial infarction	75.0	15	3	20	4
3	G.F.	64	Coronary insufficiency	75.0	24	4	14	4
4	M.L.	66	Coronary-artery disease*	65.0	9	5	12	5
5	J.C.	63	Pulmonary embolus	62.5	24	3	26	2
6	M.B.	65	Pulmonary embolus	50.0	21	3	22	2
7	N.F.	43	Myocardial infarction	62.5	23	3	21	3
8	M.L.	64	Pulmonary embolus	70.0	24	5	13	9
9	A.T.	66	Myocardial infarction	62.5	20	3	26	2
10	M.O.	62	Pulmonary embolus	50.0	19	1	24	2
11	M.F.	70	Thrombophlebitis	62.5	19	4	24	3
12	S.S.	74	Coronary insufficiency	50.0	20	4	29	2
13	R.P.	57	Myocardial infarction	50.0	20	4	9	3
14	A.C.	51	Pulmonary embolus	75.0	15	2	2	2
15	G.M.	52	Pulmonary embolus	75.0	20	3	10	†
16	E.C.	60	Pulmonary embolus; rheumatic heart disease.	60.0	16	3	6	†
17	F.R.	78	Arterial embolus	50.0	22	3	20	2
18	P.H.	74	Arterial embolus; hypertensive heart disease.	60.0	18	2	7	†
19	E.B.	68	Myocardial infarction	62.5	22	3	18	7
20	A.S.	46	Coronary insufficiency	50.0	12	3	24	2
21	L.P.	61	Coronary insufficiency	62.5	22	3	33	2
22	A.Z.	46	Coronary insufficiency	50.0	12	3	24	2
23	M.F.	71	Myocardial infarction	62.5	24	4	17	4
Group 2 (therapeutic range within 24 to 36 hr.):								
24	M.B.	60	Myocardial infarction	70.0	30	3	20	3
25	C.M.	65	Myocardial infarction	65.0	36	4	26	4
26	M.B.	73	Thrombophlebitis	75.0	36	4	20	2
27	C.H.	59	Coronary insufficiency	75.0	25	5	6	5
28	J.C.	75	Pulmonary embolus	70.0	28	2	21	5
29	F.J.	60	Myocardial infarction	75.0	31	3	31	1
30	D.O.	76	Myocardial infarction	62.5	30	4	22	3
31	M.F.	68	Myocardial infarction	75.0	32	3	20	2
32	O.F.	78	Myocardial infarction	62.5	29	5	12	4
33	E.D.	52	Thrombophlebitis	50.0	32	3	30	2
34	J.D.	57	Myocardial infarction	75.0	36	3	28	2
35	S.M.	72	Thrombophlebitis	62.5	36	3	16	3
36	R.B.	71	Myocardial infarction	62.5	36	3	28	2
37	H.O.	72	Pulmonary embolus	60.0	28	2	30	2
38	H.S.	63	Myocardial infarction	62.5	35	3	30	1
39	A.P.	58	Myocardial infarction	62.5	34	5	16	4
40	M.F.	57	Myocardial infarction	50.0	36	2	35	1
41	B.F.	44	Myocardial infarction	75.0	36	3	31	1
42	L.B.	46	Myocardial infarction	75.0	32	3	31	2
43	M.G.	57	Thrombophlebitis	50.0	35	5	14	5
44	E.F.	66	Myocardial infarction	50.0	35	3	35	1
45	M.M.	36	Thrombophlebitis	62.5	26	3	25	4
46	F.H.	67	Coronary-artery disease*	50.0	36	2	28	2
47	M.F.	58	Myocardial infarction	75.0	32	3	20	3
48	M.A.	43	Pulmonary embolus	62.5	34	3	34	2
49	L.K.	62	Myocardial infarction	62.5	35	3	23	2

*Prophylactic administration.
†Vitamin K_1 administered.
‡Only case requiring more than 48 hr.

TABLE 5 *(Concluded).*

CASE NO.	INITIALS	AGE	DIAGNOSIS	INITIAL DOSE	THERAPEUTIC RANGE			
					INTERVAL REQUIRED	PEAK EFFECT	PROTHROMBIN	DURATION
		yr.		*mg.*	*hr.*	*days*	*%*	*days*
Group 2 (therapeutic range within 24 to 36 hr.) (continued):								
50	H.W.	60	Thrombophlebitis	62.5	33	3	35	1
51	G.B.	62	Myocardial infarction	62.5	32	3	31	1
52	M.F.	87	Coronary-artery disease*	37.5	31	3	19	8
53	M.H.	78	Myocardial infarction	55.0	32	3	18	2
54	A.D.	64	Myocardial infarction	50.0	36	3	15	3
55	J.B.	66	Myocardial infarction	62.5	32	3	25	2
56	E.F.	30	Thrombophlebitis	37.5	31	3	28	1
57	A.C.	42	Thrombophlebitis	50.0	30	3	35	2
58	B.B.	47	Myocardial infarction	50.0	26	3	22	3
59	M.D.	76	Thrombophlebitis	50.0	34	3	27	2
60	M.B.	62	Myocardial infarction	62.5	36	4	15	3
61	B.B.	47	Myocardial infarction	62.5	35	3	28	2
62	M.D.	76	Thrombophlebitis	50.0	34	3	27	2
63	E.A.	60	Pulmonary embolus	62.5	32	4	16	4
64	M.T.	23	Pulmonary embolus	62.5	36	3	30	1
65	J.L.	78	Thrombophlebitis	50.0	32	2	30	?
66	W.M.	83	Thrombophlebitis	50.0	32	2	35	1
67	A.B.	61	Myocardial infarction	37.5	36	5	17	2
68	J.P.	53	Myocardial infarction	62.5	29	3	20	2
69	M.M.	63	Coronary insufficiency	37.5	34	3	13	6
70	J.A.	54	Myocardial infarction	81.25	36	3	17	2
71	A.B.	70	Myocardial infarction	56.25	36	3	34	2
Group 3 (therapeutic range within 36 to 48 hr.):								
72	M.T.	66	Myocardial infarction	60.0	48	3	30	3
73	J.M.	67	Myocardial infarction	68.0	39	3	26	1
74	L.H.	67	Pulmonary embolus	60.0	45	3	28	2
75	S.A.	68	Coronary insufficiency	75.0	46	4	18	3
76	R.B.	43	Myocardial infarction	75.0	45	3	30	1
77	R.D.	67	Myocardial infarction	62.5	40	3	29	1
78	D.D.	46	Myocardial infarction	75.0	40	3	30	1
79	M.W.	61	Thrombophlebitis	62.5	48	3	35	1
80	S.S.	67	Pulmonary embolus	60.0	44	3	28	2
81	H.S.	69	Myocardial infarction	62.5	40	4	30	2
82	H.P.	65	Coronary insufficiency	75.0	44	3	30	2
83	M.W.	58	Thrombophlebitis	62.5	49‡	3	35	1
84	H.C.	37	Myocardial infarction	75.0	41	3	34	1
85	P.S.	73	Myocardial infarction	50.0	40	3	31	1
86	J.B.	73	Myocardial infarction	50.0	41	4	29	2
87	F.K.	58	Myocardial infarction	75.0	44	3	27	1
88	A.F.	52	Coronary insufficiency	75.0	41	3	28	3
89	A.S.	61	Myocardial infarction	50.0	40	3	23	2
90	H.S.	76	Pulmonary embolus	50.0	46	4	30	1
91	M.V.	47	Coronary insufficiency	50.0	40	3	35	1
92	M.F.	65	Myocardial infarction	37.5	42	3	31	2
93	H.H.	62	Coronary insufficiency	62.5	43	3	27	1
94	A.F.	87	Thrombophlebitis	37.5	39	3	19	8
95	M.W.	60	Coronary insufficiency	75.0	39	3	27	2
96	E.B.	70	Myocardial infarction	56.25	39	3	35	1
97	L.T.	61	Rheumatic heart disease	50.0	42	3	20	1
98	E.M.	72	Thrombophlebitis	56.25	38	3	30	1
99	S.L.	83	Myocardial infarction	40	44	3	30	1
100	J.L.	57	Myocardial infarction	50	40	3	34	1

*Prophylactic administration.
†Vitamin K_1 administered.
‡Only case requiring more than 48 hr.

prothrombins were between twelve and fourteen seconds. These were considered as 100 per cent prothrombin. Results were reported in seconds and converted to percentage of prothrombin by means of a graph relating prothrombin time in seconds to prothrombin percentage. Initially, we determined prothrombin values at four, eight and twelve hours; later, twenty-four-hour intervals were used, except in the few cases in which phytonadione (vitamin K_1) was used.

Phytonadione (Mephyton) was administered parenterally to counteract excessive hypoprothrombinemia (level of 10 per cent or below) or hemorrhage, when either appeared. In some cases of excessive hypoprothrombinemia, phytonadione was not used — the prothrombin level was allowed to rise spontaneously.

We did not regard shock as a contraindication to Coumadin therapy. Indeed, we believe that these patients can benefit from anticoagulant therapy.

Results

We personally administered the drug to 105 patients. But only 100 patients with the conditions shown in Table 1 are reported on, since the initial response in 5 patients was inadequate and the omission of these from the tabulation did not appear to affect the conclusions.

Initial Dose

The initial dose varied from 37.5 mg. to 81.25 mg. The dose distribution appears in Table 3. The patients were grouped according to the time required to reach the therapeutic range. The averages are presented in Table 4, and the detailed data in Table 5. We believe that a listing of the individual responses gives a truer picture than reporting average results. We did not attempt to ascertain the time required for the level to return to normal after the initial dose because maintenance therapy was instituted. However, we have examples of five, eight and nine days' duration of effect after the initial dose.

A good therapeutic response to the initial dose resulted in all patients within forty-eight hours: 23 per cent responded within twenty-four hours, 71 per cent within thirty-six hours, and 100 per cent within forty-eight hours. This inadequate response was due to insufficient initial dosage — since subsequent doses brought these patients into the therapeutic range (Fig. 2). Our experience indicates that there need be no great fear of hemorrhage from the first dose in patients who present no known contraindications to anticoagulant therapy.

Contrary to the observations of Wolff and his associates,[20] we did not find that the initial dose had to be lowered when the patients were vomiting. This is in accord with the reports of Shapiro[13,14] and de Nicola.[21]

Discussion

Coumadin Sodium is a hypoprothrombinemia-inducing agent of relatively rapid action. It yields a desired hypoprothrombinemic effect as quickly as Tromexan, but the prothrombin-inducing action is more prolonged and more stable. Our results indicate that Coumadin Sodium is a more predictable and effective hypoprothrombinemia-inducing agent than Hedulin. Kruesi and Schilling[22] reported that only

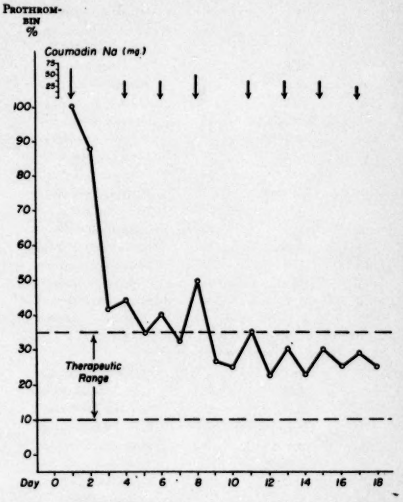


Figure 2. *Delayed Effect of Inadequate Initial Dosage. This case illustrates a delayed therapeutic response to the initial dose but a satisfactory response to continued intermittent dosage.*

6.9 per cent of patients receiving Hedulin, 150 to 400 mg., responded in twenty-four hours and that only 55.6 per cent reached the therapeutic range in forty-eight hours.

We found that 100 per cent of recipients responded by a lowering of prothrombin to our therapeutic range within forty-eight hours; 23 per cent responded within twenty-four hours, and 73 per cent within thirty-six hours. No patient failed to respond. The few who failed to respond adequately to the initial dose received insufficient dosage as indicated by a satisfactory response to subsequent smaller doses. Patients who reached the therapeutic range earlier remained in the therapeutic range for a longer period (Fig. 3). This action is presumably due to sensitivity of the patient to the anticoagulant. These data suggest a pattern from which subsequent maintenance doses may be estimated. Patients who reach the

therapeutic range within a twenty-four-hour period will, in general, require the lower doses for maintenance of therapeutic hypoprothrombinemia. Conversely, those who respond after twenty-four hours may require somewhat larger doses for maintenance. However, despite these fluctuations in response to the initial dose, little difficulty was apparent in the selection of an individual daily maintenance dose, which proved to be remarkably constant from day to day in the same patient.

One patient with myocardial infarction with shock received 62.5 mg. initially by mouth and daily doses of 6.25 mg. thereafter (Fig. 4). A good therapeutic result was obtained.

Maintenance Dose

The first maintenance dose was given at the time when the effects of the initial dose were being dissipated as indicated by a rise of prothrombin level

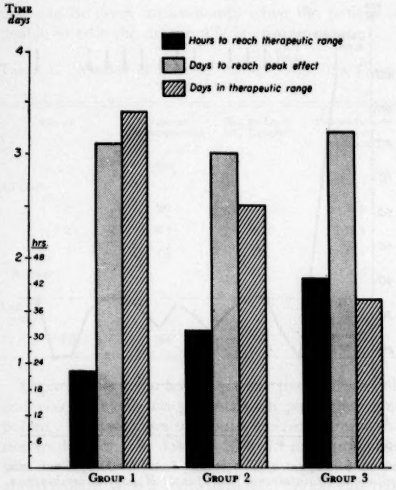


Figure 3. *Relation of Initial Dose to Time to Reach the Therapeutic Range, Peak Effect and Duration of Therapeutic Hypoprothrombinemia (Data from Table 4). An early response is followed by a longer duration in the therapeutic range.*

in the therapeutic range; subsequent doses were given similarly. Figures 5 and 6 represent the response to initial and subsequent maintenance doses by the intermittent and continuous scheme of dosage.

Maintenance of therapeutic hypoprothrombinemia was relatively easy with Coumadin. This was determined by the percentage of days of "escape" from the therapeutic range for all patients (Table 6). These figures indicate that the patients were under anticoagulant control for about 90 per cent of the days while receiving the drug. The "escape" periods, which did not greatly exceed the upper limit of the therapeutic range, occurred mainly with the intermittent schedule. Dosage by the continuous method yielded fewer "escape" periods, and this is now our method of choice. As we gained experience in handling the drug, we found that the "escape" periods could be further reduced. This is illustrated by our

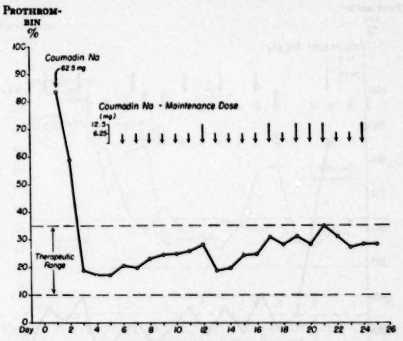


Figure 4. *Hypoprothrombinemia-Inducing Effect of Coumadin Sodium in Myocardial Infarction with Shock. Note the steady level of therapeutic hypoprothrombinemia with relatively constant daily doses.*

experience with the last 21 patients given the drug. In these cases, in which only continuous maintenance doses were given, the "escape" periods were reduced to 7 per cent of total days of therapy, indicating that a satisfactory level of anticoagulation had been achieved for 93 per cent of the days under therapy. Shapiro,[23] who had championed the intermittent dose method for Dicumarol and cyclocumarol, has reported recently that Coumadin is ideally suitable for continuous dosage — an opinion that is in accord with our experience.

Since a comparison of new congeners of Dicumarol has been made with this as a standard, we have collected data on several patients who had previously received Dicumarol. Figure 7 shows 1 of several such cases. A larger series will form the subject of a separate report.

Hemorrhage and Excessive Hypoprothrombinemia

Hemorrhage occurred in 3 postoperative surgical cases in this series — 2 were of major proportions. All 3 patients responded to phytonadione, 50 mg. Petechiae occurred in 2 patients, disappearing when the drug was withheld for several days. Three patients showed levels of prothrombin time below 10 per cent, but no signs of hemorrhage were observed. They were

given small doses of phytonadione, which promptly elevated the prothrombin to safe levels.

One of the patients with major hemorrhage had undergone a suprapubic prostatectomy. He had a pulmonary embolism nine days after operation, for which 62.5 mg. of Coumadin Sodium was given intravenously, followed by two oral doses of 25 mg. each at about five-day intervals. Five days after the second dose, bleeding from the prostate bed occurred, after

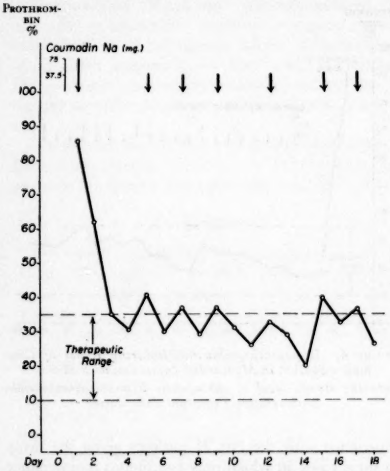


FIGURE 5. *Effect of Coumadin Sodium by the Intermittent Method of Dosage.*

Note the smoothness of the hypoprothrombinemia within the therapeutic range. (Compare with Figures 4 and 6 on continuous dosage, which yields a smoother curve of therapeutic hypoprothrombinemia.)

an indwelling catheter was removed. Phytonadione, 50 mg., administered intravenously, was followed by cessation of the bleeding and return to normal prothrombin five hours later (Case 1, Fig. 8).

A second patient with peritonitis with an abdominal fistula bled from the fistulous tract after receiving 75, 50 and 37.5 mg. of Coumadin successively in the course of ten days. A prothrombin level of 10 per cent, with no bleeding, appeared after the initial 75-mg. dose; 5 mg. of phytonadione restored the prothrombin time to 65 per cent. Three days after the 37.5-mg. dose of Coumadin bleeding from the fistulous tract appeared, which was corrected in six hours by phytonadione, 50 mg. (Case 2, Fig. 8).

The third patient, who was subjected to a partial colectomy and who was provided with an indwelling catheter, had gross hematuria, with a prothrombin level of 6 per cent, after receiving 60 mg. of Coumadin. Phytonadione, 50 mg., stopped the bleeding and restored the prothrombin time to normal six hours later (Case 3, Fig. 8).

Three cases of low prothrombin levels, without bleeding, presented an opportunity to try the effect of small doses of phytonadione. Prothrombin times of 6, 5 and 10 per cent responded to safe levels of hypoprothrombinemia after administration of phytonadione, 4, 10 and 10 mg., respectively (Fig. 9). All 3 patients received the drug by an intermittent schedule. Therapeutic hypoprothrombinemia was readily reinduced by subsequent administration of Coumadin. These results are in contrast to our previous experience with Dicumarol, for which longer refractory periods were the usual pattern.

No case of bleeding or excessive hypoprothrombinemia occurred in nonsurgical patients or in those receiving smaller daily maintenance doses (6.25 to 12.5 mg.) by the continuous method.*

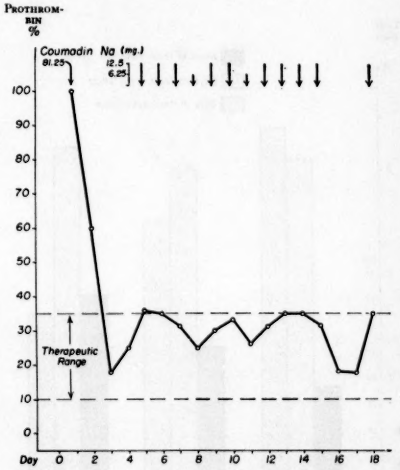


FIGURE 6. *Effect of Continuous Small Doses of Coumadin Sodium in Maintaining Therapeutic Hypoprothrombinemia. Note the predictability of the response.*

Long-Term Therapy

We have had the opportunity of conducting long-term prophylactic administration for ten, eleven, eleven and eighteen months on 4 patients. These trials suggest that the maintenance of Coumadin dose is easier to control than that of Dicumarol.

Clinical Data

A total of 8263 mg. of Coumadin was given as

*The smaller doses were aliquots of the 25-mg. quarter-scored tablet, which was not always convenient to divide. We have been advised that a 10-mg. single-scored tablet will soon be available.

maintenance doses to 100 patients over a period of eight hundred and sixty patient days. The average daily maintenance dose was 9.6 mg.—a figure remarkably close to that previously reported by Pollock.[18]

The anticoagulant action of the drug accomplished a satisfactory initial anticoagulant effect. No toxic side effects were noted. No deaths due to the drug occurred. No patient had pulmonary embolism, thrombophlebitis or arterial embolism not existing previously while under the anticoagulant therapy. No complications, other than the controllable bleeding in 3 cases, occurred while the drug was being used. We regard bleeding as an extension of the pharmacologic action and not as a toxic side reaction.

We found no essential difference when the drug was given intravenously or orally. Absorption of the drug must be complete, as evidenced by the animal experiments cited and by the results discussed above. Hence, oral administration is the method of choice. However, the availability of a synthetic anticoagulant that can be given intravenously when the patient is unable to take the drug orally is advantageous.

TABLE 6. *Number of Days of "Escape" from the Therapeutic Level.*

GROUP	PERIOD OF ADMINISTRATION	NO. OF DAYS OF "ESCAPE"	PERCENTAGE OF DAYS OF "ESCAPE"
	days		
All cases:			
1	387	35	9.0
2	879	92	10.5
3	535	68	13.1
Average			10.9
Last 21 cases:			
1-3	366	28	7.7

Heparin was given less frequently than Dicumarol, and was used only on patients with pulmonary embolism. In these cases we could limit its administration to three or four doses of 50 to 75 mg. during the first twenty-four hours. Thus, the availability of an anticoagulant with a short induction period can represent a considerable economy to the patient and to the hospital routine.

Maintenance of smooth levels of hypoprothrombinemia proved to be relatively easy. When the initial dose proved to be inadequate, supplementary doses at a lower level almost invariably depressed the prothrombin so that a satisfactory therapeutic effect was obtained.

We did not attempt to determine the number of days for the effect of a single initial dose to return to normal prothrombin, since maintenance doses were given before the full effect of the initial dose was expended. Reference to Table 5 shows examples of duration of therapeutic hypoprothrombinemia for five, seven, eight and nine days. Our results indicate that the length of therapeutic effect of the first dose was related to the early onset of effect. Hence, as with other anticoagulants, the course of the therapy should be followed by frequent prothrombin-time determinations during the acute phase of a thromboembolic episode.

The average initial dose, time required to achieve the therapeutic range, time to reach maximum therapeutic effect and length of therapeutic effect appear

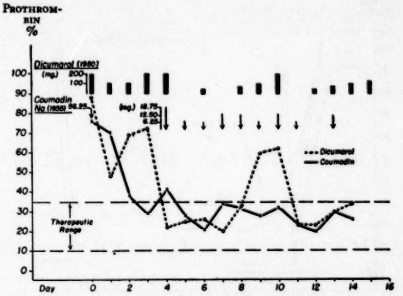


FIGURE 7. *Anticoagulant Effect of Dicumarol and Coumadin Sodium in the Same Patient.*
Note the more stable level of hypoprothrombinemia obtained with Coumadin.

in Tables 4 and 5. In terms of average, the initial dose was about 60 mg. for all three groups; the time to produce a therapeutic effect was twenty-two, thirty-two and forty-three hours, and the length of therapeutic effect was three, four, two and a half and one and six-tenths days (Fig. 3). The time required to reach maximum therapeutic effect was similar in all three groups. We agree with Clatanoff et al.[17] that generally 75 mg. may be the maximum dose.

The average daily maintenance dose by either the intermittent or the continuous method was 9.6 mg. The periods of "escape" from maintenance doses were low; patients receiving the drug were in a satisfactory state of anticoagulation for about 90 per cent of the time while they received the drug. This performance was bettered as our experience with the drug continued. The "escape" periods occurred mostly in patients receiving the drug by the intermittent method — the continuous method was used in all our later cases.

There appears to be a rough correlation between body weight and initial dose of 1 mg. per kilogram; there appears to be no correlation between body weight and maintenance dosage. Nevertheless, for each patient the maintenance dose was remarkably constant. The individual daily maintenance dose, usually between 6.25 and 12.5 mg., could easily be determined after only a few trials. Occasionally, a

few patients departed from these usual doses. The ease of forecasting maintenance doses is shown in Figures 4, 5 and 6 on patients receiving Coumadin alone and in Figure 7 on a patient who received Dicumarol and Coumadin at different periods. Although the initial dose of Coumadin provides a relatively long duration of therapeutic effect, the effect of a maintenance dose is generally dissipated about two days after the last prothrombin determination.

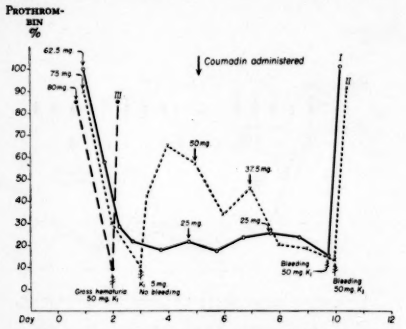


FIGURE 8. *Effect of Phytonadione (Vitamin K_1) in Counteracting Bleeding from an Anticoagulant.*

The only cases of severe, but controllable, hemorrhage were noted in 2 patients who had undergone major surgery. Hemorrhagic phenomena did not appear in the patients who received the drug for medical indications, except for the 2 cases of petechiae noted.

The drug is relatively quickly counteracted by phytonadione. Administration of vitamin K_1, intravenously, restored prothrombin time to safe levels and led to clinical cessation of bleeding in the few cases in which bleeding occurred.

The results of both intravenous and oral administration closely parallel those of Shapiro,[13,14] Clatanoff and his associates[17] and Pollock.[18] Coumadin Sodium, in the light of these and the previously reported experiences, approaches more nearly the ideal hypoprothrombinemia-inducing drug. It yields a prompt anticoagulant effect with a high degree of predictability, a stable level of hypoprothrombinemia is easily maintained, it showed no adverse toxic side effects, and it is readily counteracted by phytonadione, if occasion demands. The sensitivity to vitamin K_1 makes it a more ideal drug for patients receiving anticoagulants who have to undergo surgery.

SUMMARY AND CONCLUSIONS

Coumadin Sodium (Link's warfarin sodium) was used intravenously and orally as the hypoprothrombinemic inducing and maintaining agent in 100 cases requiring anticoagulant therapy. The induction of therapeutic hypoprothrombinemia (level of 35 to 10 per cent) was relatively prompt. The use of heparin was limited to patients with pulmonary embolism — these patients received only about three or four doses of heparin. The initial dose averaged about 60 mg., and the daily maintenance dose by the continuous or intermittent method, based on daily prothrombin determinations, was about 10 mg. The maintenance dose, which was readily established, was generally consistent from day to day in the same patient. Fewer periods of "escape" from the therapeutic range occurred than with the other anticoagulant drugs we used.

Hemorrhagic phenomena, attributable to the drug, occurred in 5 cases (3 of bleeding and 2 of subcutaneous petechiae). The bleeding occurred only in patients who had undergone surgery, and cleared promptly after administration of phytonadione. Smaller doses of phytonadione raised the prothrombin from 5 per cent without bleeding to safer levels in 3 cases. No deaths ascribable to the drug appeared.

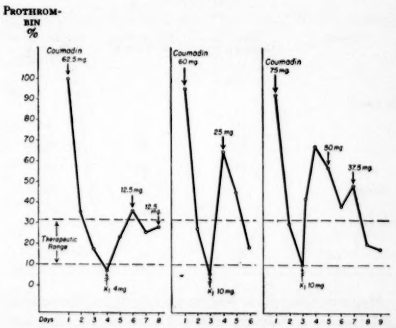


FIGURE 9. *Effect of Small Doses of Phytonadione (Vitamin K_1) in Counteracting Low Prothrombinemia without Bleeding.*

These experiences, taken in conjunction with the reports that have already appeared, permit the conclusion that Coumadin (warfarin) Sodium is a more nearly ideal anticoagulant drug than any of its congeners now available. The drug deserves a wide clinical application in thrombotic and thromboembolic disorders.

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NONSPECIFIC GRANULOMATOUS INFLAMMATION OF THE GASTROINTESTINAL TRACT*

Report of a Case

CAPTAIN PERRY B. MILLER, MC, USAF,† DAVID J. SANDWEISS, M.D.,‡ AND HARRY SHWACHMAN, M.D.§

DETROIT, MICHIGAN, AND BOSTON, MASSACHUSETTS

IN their classic description of regional ileitis in 1932, Crohn, Ginzburg and Oppenheimer[1] expressed the opinion that this condition involves the terminal ileum. Shortly thereafter it was shown that this nonspecific granulomatous process may involve the colon, jejunum,[2-5] and more rarely the duodenum[6-18] and stomach.[7,12,17,19] In 1954 Heffernon and Kepkay[7] described a case of chronic nonspecific segmental inflammation of the esophagus, stomach, duodenum, jejunum and ileum.

The patient in the case presented below had widespread nonspecific granulomatous inflammation of the stomach, duodenum, jejunum, ileum and colon in which the pathological findings resembled in many respects those seen in patients with regional enteritis. Clinical studies, including numerous roentgenograms, were insufficient to suggest the diagnosis, which was finally made three years after the onset of symptoms, after an exploratory laparotomy.

CASE REPORT

A 6-year-old boy first complained of nausea, vomiting, vague abdominal pain and fever in 1948. Physical examination and laboratory studies were negative. He recovered rapidly and was well until January, 1950, when he and several of his siblings had diarrhea. Stool cultures were negative although the father and 2 siblings were found to have bacillary dysentery. After 3 months of intermittent diarrhea the patient began to complain of recurrent short attacks of periumbilical pain that were unlike the crampy pain associated with the diarrhea. The pain could be relieved with milk or by pressure of his hand on the abdomen. Roentgenograms of the gastrointestinal tract in May showed a narrowing in the prepyloric antrum that suggested a congenital adhesive band. The possibility of inflammatory changes in the prepyloric antrum was also mentioned by the roentgenologist (Dr. Vincent C. Johnson, Harper Hospital, Detroit). Study of the small bowel and colon revealed no abnormalities.

The child continued to have intermittent episodes of epigastric and periumbilical pain associated with nausea, occasionally with vomiting and frequently with diarrhea. During October, 1950, he was at Harper Hospital, Detroit, on a strict Sippy ulcer regimen for a period of nearly three weeks. No gross blood was observed in the stool at any time; the guaiac test for occult blood varied from negative to ++. Figure 1 shows the narrowing of the gastric antrum at this time. He was asymptomatic during the period of hospitalization and gained 3.2 kg. (7 pounds). However, three weeks after discharge from the hospital, his symptoms recurred. He soon refused to eat solid foods and to attend school. In view of a considerable degree of sibling incompatibility he was sent to live with his grandparents in Florida with the hope that an environmental change would restore his health. During the several months he was away from home he improved. However, upon his return home in June, 1951, abdominal pain and diarrhea recurred.

In August, 1951, the patient was admitted to the Children's Medical Center, Boston, for study. Physical examination was negative. He had recently lost weight (Fig. 2). Laboratory examination revealed a red-cell count of 4,230,000, with a hemoglobin of 12.4 gm. per 100 ml., and a white-cell count of 10,550, with a normal differential. The tuberculin test was negative in a 1:1000 dilution. Stool cultures were negative. Many guaiac tests for occult blood were performed, with an occasional positive test. The total serum protein was 6.8 gm. per 100 ml. Gastric analysis showed no free hydrochloric acid. Gastrointestinal studies were thought to show a gastric ulcer. The patient was discharged with a diagnosis of gastric ulcer. A bland diet was recommended.

*From the Department of Internal Medicine, Harper Hospital, Detroit, and the Children's Medical Center, Boston.

†Chief resident in medicine, Harper Hospital, Detroit, Michigan.

‡Physician, Harper Hospital; associate physician, Receiving Hospital; chief of Section on Gastroenterology, Sinai Hospital, Detroit, Michigan.

§Assistant professor of pediatrics, Harvard Medical School; physician, and chief of Chronic Nutrition Clinic, Children's Medical Center.

At home recurrent vomiting, diarrhea, and abdominal pain accompanied by fever again developed. He was readmitted to the Children's Medical Center in September. While in the hospital he had a low-grade fever (the temperature did not go above 101°F.). He was again placed on a strict ulcer regimen, which brought about marked improvement. His appetite was better, the abdominal pain disappeared, and the stools approached normal in number and consistence. He was discharged on October 5 and advised to continue the ulcer regimen at home. A few days later diarrhea, this time accompanied by gross blood in the stools, and fever, with a maximum temperature of 104.2°F., and a biopsy of the stomach wall was obtained. A Meckel diverticulum was discovered and excised.

Microscopical examination of the stomach, Meckel diverticulum and appendix revealed an ulcerative granulomatous process containing plasma cells, multinucleated giant cells and large mononuclear cells (Fig. 3). Numerous crypt abscesses were seen in the sections of the diverticulum. Crypt abscesses with granulomatous reaction were also found in the stomach.

The patient recovered rapidly. Repeat x-ray studies showed a well functioning gastroenterostomy as well as the antral deformity previously described. No recognizable ab-

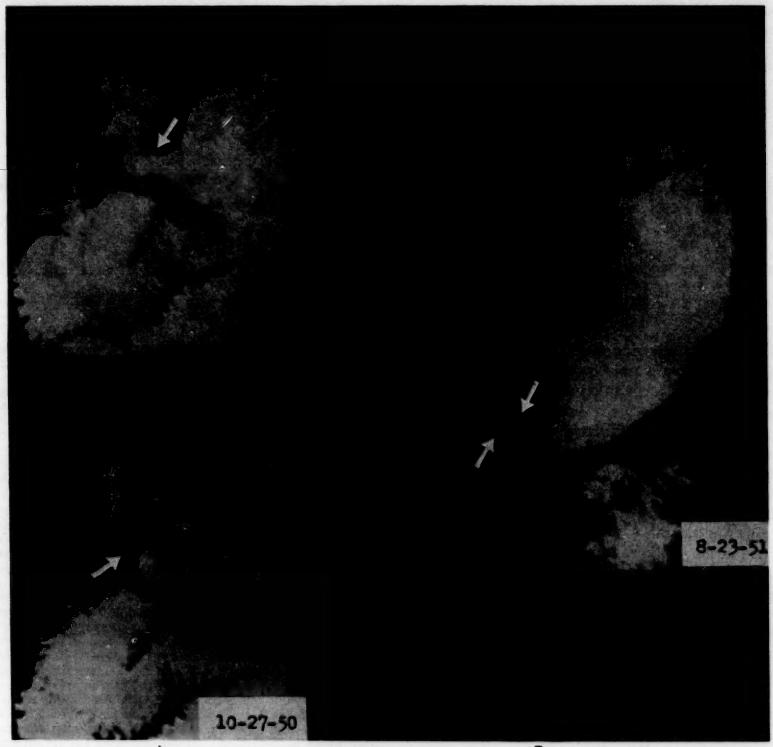

FIGURE 1. *Roentgenograms of the Stomach, Showing Annular Narrowing of the Distal Portion of the Gastric Antrum* (A), *with an Increase in the Annular Narrowing of the Prepyloric Antrum Ten Months Later* (B).

again developed. He was readmitted to the hospital on October 8, and after a short course of chloramphenicol therapy the symptoms abated. An exploratory laparotomy was performed by Dr. Robert E. Gross on October 25. Much more extensive disease was found than had been anticipated. The stomach, duodenum, small intestine and colon were found to be involved in a process that had caused marked thickening of the intestinal wall in scattered areas. In addition there was widespread lymphadenopathy. A gastroenterostomy and an appendectomy were performed, normalities of the small bowel were seen despite the findings at operation. He was discharged and remained well for several months. However, diarrhea again developed in March, 1952, and he was readmitted to the Children's Medical Center in April. He now weighed 2.7 kg. (6 pounds) more than on the previous admission. He improved rapidly.

During the past 2 years he has had relatively few gastrointestinal symptoms and has gained 1.8 kg. (4 pounds) in weight. His present weight is 35.4 kg. (78 pounds), and

his height is 146 cm. (57½ inches). There is no digital clubbing, and the spleen is not palpable. A complete gastrointestinal x-ray series in June, 1955, revealed a well functioning gastroenterostomy with no barium passing into the antrum of the stomach or the duodenum, a narrowing and distortion of the terminal ileum, a distortion of the cecum and a slight irregularity in the mucosal pattern of the colon.

Discussion

This case exemplifies the difficulty frequently encountered in the diagnosis of regional enteritis before operation. Despite the widespread disease noted at laparotomy the preoperative findings were of little help in elucidating the nature of the illness. Numerous roentgenograms of the gastrointestinal tract showed changes only in the stomach that were variously interpreted as due to an ulcer, a congenital adhesive band or possibly to an inflammatory process.

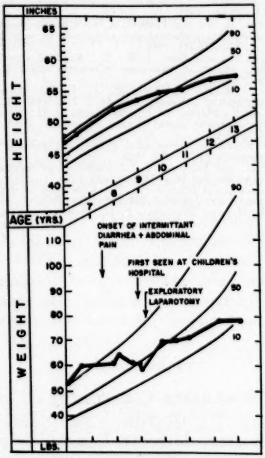

Figure 2. *Growth Chart.*
The percentiles are based on studies of Harold C. Stuart, of the Harvard School of Public Health, and prepared for use at the Children's Medical Center.

The symptoms presented by this patient were nearly similar to those described by Comfort et al.[12] for patients with regional enteritis involving the duodenum: distress in the upper abdomen intensified by food and accompanied by loss of weight and strength and by nausea and vomiting; diarrhea, steatorrheal and episodic in type; gastric retention; and evidence of malabsorption. Later reports[16,18] have described a similar clinical picture. In the majority of cases involvement of the duodenum results in retention or obstruction, which necessitates some type of short-circuiting procedure. In the 14 cases available for review[7-9,12-18] 11 patients had short-circuiting procedures; 8 of these were gastroenterostomies,[9,12,13,15,16] and 3 were duodenojejunostomies.[7,8,16] In the 6 cases with involvement of the stomach (5 verified by gastric biopsy)[7,12,17,19] comparable lesions were found elsewhere in the gastrointestinal tract. In the case reported by Ross[19] pathologic changes were found in the ileum and colon. In the 2 cases described by Comfort et al.[12]

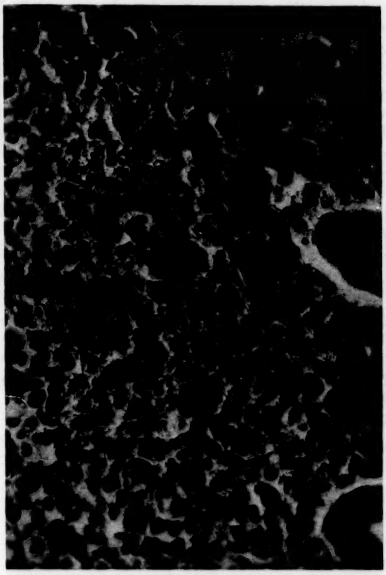

Figure 3. *Histologic Appearance of the Stomach (X432). The granulomatous reaction consists of plasma cells, multinucleated giant-cell forms, lymphocytes and large mononuclear elements.*

the inflammatory process began in the stomach and duodenum and later spread to the jejunum in 1 and to the entire small bowel in the other. Heffernon and Kepkay[7] found chronic nonspecific segmental inflammation of the esophagus, stomach, duodenum, jejunum and ileum. In 2 cases presented by Martin and Carr[17] the stomach, duodenum and ileum were involved; in 1 of their cases terminal ileitis was first demonstrated at operation, and subsequently upper gastrointestinal x-ray examination showed involvement of the stomach and duodenum.

It appears that the histologic picture found in the stomach of this patient resembles the typical findings of regional enteritis except for the crypt abscesses. The microscopical examination of the Meckel diverticulum and appendix also showed a nonspecific

granulomatous inflammation. The development of a widespread granulomatous reaction is characteristic of regional ileitis and not of ulcerative colitis.[20] On the other hand crypt abscesses, such as were seen in the ileum in this case, have been described by Warren and Sommers[20] as a constant early lesion of ulcerative colitis. Comfort et al.[12] stated that in their case in which both terminal ileum and stomach were involved the identical microscopical picture was seen in both regions — that is, ulceration, granulomatous inflammation and inflammation and obstruction of lymph vessels.

Since failure to grow may be the presenting complaint[22] the effect of this chronic process in the growth of the patient described above is worth pointing out. The disease probably began at about the time the weight curve flattened out. The weight lost over the years is considerable, declining from the 90 percentile weight at six and a half years to below the 10 percentile level at thirteen years of age. The height showed a delayed and comparable decline.

Summary

A case of nonspecific ulcerative granulomatous enteritis with involvement of the stomach, duodenum, jejunum, ileum and colon is described. It illustrates the difficulties encountered in both the clinical and the pathological diagnoses in cases of this type.

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15. Bookplate of John Mark Gourgas, corresponding secretary of the committee for vaccination of the town of Milton. The bookplate is affixed to the Library's copy of *A Collection of Papers Relative to the Transactions of the Town of Milton in the State of Massachusetts to Promote a General Inoculation of the Cow Pox, or Kine Pock, As a Never Failing Preventive against Small Pox Infection* (Boston: J. Belcher, 1809).

ACUTE RENAL INSUFFICIENCY COMPLICATED BY SEVERE HYPOXIA*

Observations on the Artificial Kidney As a Blood Oxygenator

LIEUTENANT COMMANDER RAYMOND H. WATTEN, MC, USN,†
LIEUTENANT COMMANDER PAUL D. DOOLAN, MC, USN,‡ MAXINE E. HUTCHIN,§
CAPTAIN ROBERT O. CANADA, MC, USN,¶ AND HAROLD A. HARPER, PH.D.‖

OAKLAND AND SAN FRANCISCO, CALIFORNIA

ACUTE renal insufficiency is a syndrome in which the ultimate clinical manifestations depend on such varied factors as the nature of the precipitating event, the duration of the phase of renal excretory inadequacy, the presence or absence of complicating conditions, the duration and intensity of the catabolic response and the over-all wisdom of the therapeutic program. The case presented below illustrates well the absolute importance of these variables. Furthermore, it provided valuable data for a study of the changes in blood oxygen content during hemodialysis.

METHODS

Dialyses were performed with the Kolff–Merrill type of artificial kidney.[1] The blood urea nitrogen concentrations were determined manometrically by the method of Van Slyke and Kugel,[2] and the blood oxygen content by the method described by Hawk et al.[3] Total body water was measured by tritium dilution.** The osmolarities of the blood and urine were measured by the freezing-point method, the Fiske osmometer being used. Standard laboratory methods were employed in other analyses.

CASE REPORT

R.M.B. (U.S.N.H. 255065), a 30-year-old man, sustained crushing injuries to his pelvis in an automobile collision on October 8, 1955. Despite transfusions of whole blood and dextran he remained in shock until 3 lacerations in the bladder and an avulsion of the prostatic urethra were repaired approximately 11 hours later at the Highland Alameda County Hospital, Oakland, California. X-ray studies later revealed fractures of both pubic rami and the right acetabulum. After the diagnosis of acute renal insufficiency was established a conservative fluid regimen was instituted on the 3d day, and on the 6th day he was transferred to the United States Naval Hospital, Oakland.

A résumé of the patient's course is provided by Figure 1, and supplementary laboratory data are presented in Table 1. Biochemically, the pattern of progression was typical, but 3 observations are worthy of note:

The 1st point is that 6 dialyses were performed, 4 for the treatment of uremia (on the 7th, 11th, 21st and 32d days). Two of these dialyses (on the 21st and 32d days) involved the calculated risk of producing an increase in gastrointestinal bleeding, which was a factor intensifying the azotemia. No increase in bleeding was noted during either procedure, but 24 hours after dialysis on the 21st day the patient bled massively. Protamine sulfate had been given in adequate amounts. The other 2 dialyses

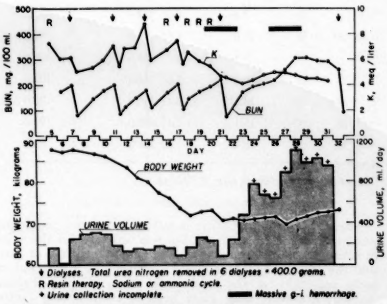

FIGURE 1. *Salient Biochemical and Clinical Events during the Survival Period.*

(on the 14th and 17th days) were for uremia complicated by potassium intoxication. Control of serum potassium concentration had been facilitated by rectal administration of sodium cycle carboxylic resin on the 5th, 16th, and 18th days, but when the serum sodium concentration reached 153 milliequiv. per liter, ammonium cycle carboxylic resins were substituted. The resins were given via a gastric tube on the 19th and 20th days, but persistent vomiting precluded their further use. After dialysis for potassium intoxication on the 14th day and for several days thereafter, serial electrocardiograms revealed the following arrhythmias: supraventricular tachycardia, with atrioventricular disassociation and interference, nodal and ventricular ectopic contractions and sinus bradycardia — all interspersed with periods of normal sinus rhythm. In addition a loud, pericardial friction rub was audible on the 16th day, and thereafter its intensity seemed to parallel the degree of uremia. Electrocardiographic changes consistent with pericarditis did not appear until the 28th day, some 12 days after the rub was heard.

In the 6 dialyses a total of 400 gm. of urea nitrogen was recovered in the dialysate, and during the 1st 8 days of diuresis a quantity of urea nitrogen in excess of 38 gm. was excreted. This 438 gm. represents a conservative underestimation of the total nitrogen lost since it does not include either that lost from the skin and gastrointestinal

*From the Metabolic Research Facility, United States Naval Hospital, Oakland.
The opinions and assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

†Medical officer, Metabolic Research Facility, United States Naval Hospital, Oakland.

‡Chief of research and director, Metabolic Research Facility, United States Naval Hospital, Oakland.

§Chief biochemist, Metabolic Research Facility, United States Naval Hospital, Oakland.

¶Chief, Medical Service, United States Naval Hospital, Oakland.

‖Associate professor of physiologic chemistry, University of California School of Medicine, San Francisco, and civilian consultant in biochemistry, United States Naval Hospital, Oakland.

**Performed in the laboratory of W. E. Siri, Donner Laboratory, University of California, Berkeley.

tract or the amount that would have been excreted before the blood urea nitrogen returned to normal levels. If it is assumed that urea nitrogen accounts for 90 per cent of total nitrogen, the recovery of 438 gm. indicates that a catabolism of 438 x 30* x 1.1, equaling 14,454 gm. of lean tissue, occurred. During the 32 days of his illness the patient had lost 15.5 kg. in body weight. The weight loss does not accurately reflect the decrease in lean body mass since the decrease was partially obscured by an increase in relative hydration. This increase is apparent from the result of a measurement of the total body water on the 23d day that was found to be 72.5 per cent of the total body weight. Despite these limitations the calculations given above provide a measure of the intensity of the catabolic response.

Before the episode of anoxia on the 10th day urinary volume had shown small but consistent increments. From the 10th through the 12th day it decreased, and one might speculate that additional renal damage had been inflicted by the anoxia. Apparently, prolonged and severe anoxia can cause serious renal damage.[5] This may well have been a factor in prolonging the oliguria.

Thirdly, diuresis began on the 23d day, as manifested by progressive increments in urinary volumes in excess of 500 ml. per day. By the 29th day the urinary osmolarity exceeded that of the plasma (Table 1), and on the following day the blood urea nitrogen began to fall. Death on the 32d day was considered to be nonrenal and was due to massive atelectasis after aspiration of blood from a bleeding area in the tracheotomy wound. At autopsy

TABLE 1. *Supplementary Data.*

DAY	CREATININE	SODIUM	CHLORIDE	CARBON DIOXIDE	HEMATOCRIT	PLASMA	URINE
	mg./100 ml.	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	%	*milliosmols*	
7*	15.1	130.0	87.0	16.5	30.0	334	
	7.0	139.0	104.0	20.3	30.0	310	
11*	15.5	136.0	95.0	17.0	30.0	348	
	7.9	140.0	104.0	18.3	27.0	311	
17*	16.4	153.0	98.0	25.7	31.5	393	
	9.4	152.0	104.0	24.6	34.0	339	
21*	17.6	146.0	91.0	23.2	24.5	372	
	7.1	146.0	108.0	22.5	27.3	319	
23	10.9	143.0	102.0	18.3	35.0	349	347
24	12.1	140.0	96.0	19.4	35.0	350	331
28	15.1	139.0	92.0	13.8	34.0	401	393
29	13.7	138.0	90.0	17.0	37.0	395	402

*Values obtained before & after 4 dialyses.

Secondly, no explanation is available for the prolonged period of oliguria. Dehydration was unlikely, for the ratio of urine to plasma osmolarity was consistently 1.0 or less, and the total body water was 51.2 liters (72.5 per cent of body weight) on the 23d day, when diuresis began. Anoxia, however, may have been a contributing factor since the patient's course was complicated by episodes of severe respiratory inadequacy. On the 10th day he aspirated gastric contents during several generalized convulsive seizures. After this a tracheotomy was done, and large amounts of bile-stained gastric juice were aspirated. He remained anoxic, with marked respiratory difficulty, until dialysis 2 hours later. During dialysis his condition improved dramatically; cyanosis disappeared, and he regained full consciousness. Minutes after the procedure was terminated increasing dyspnea and tachycardia were noted. Examination of the chest revealed signs consistent with atelectasis of the right lower lobe, and crepitant rales were audible over the rest of the lung fields. It was thought that the respiratory difficulties were on the basis of impaired alveolar gas exchange resulting from aspiration pneumonitis and atelectasis. This conclusion was supported by the results of arterial blood oxygen determinations over the following 3 days (Table 2). With postural drainage, frequent tracheal aspiration, nebulized Alevaire and infusion of 600 ml. of settled red cells, there was slow but definite improvement in ventilation (Table 2).

*The chemical composition of normal adult lean tissue is remarkably constant throughout mammalian species. Since the nitrogen content is included in this constant relation, it is possible to calculate the amount of lean tissue lost or gained from a knowledge of the nitrogen balance. The factors various investigators have used in this calculation vary between 30[4] and 33.4.[5] We have chosen the value 30 arbitrarily for purposes of illustration, being well aware of the limitations of such calculations in abnormal situations.

there was atelectasis of all lobes of the lung except the right upper and middle lobes, which were congested and edematous. There was an intense fibrinous pericarditis and dilatation of the heart. The kidneys were enlarged, and microscopical examination showed diffuse nephrosis, with minimal tubular regeneration. Both ureters were patent, without sign of obstruction.

DISCUSSION

Certain aspects of one of the most interesting problems that this patient presented — namely, hypoxia — will be discussed briefly. As a result of aspiration pneumonitis, he was moribund before the second dialysis. During the procedure he improved dramatically, and within two or three hours the cyanosis had cleared and he had regained consciousness. The improvement occurred much sooner and was more dramatic than could be explained by clearing of the uremia alone; in addition, there was an abrupt deterioration immediately upon termination of the procedure. It was subsequently shown that hypoxia was an important factor in this clinical deterioration (Table 2), and it was therefore reasoned that the marked improvement observed during dialysis may have been due, in part, to the increased oxygenation of the patient's blood, during extracorporeal circulation.

Although it is well known that dark blood becomes

red in passage through the artificial kidney[7] and that oxygen readily diffuses through cellophane membrane,[8] we are unaware of any quantitative studies on the changes that may occur in blood oxygen content during dialysis. The blood oxygen content was therefore measured at various intervals in four subsequent dialyses (Table 3). On the 14th, 17th and 32d days, it will be noted, the oxygen content of the blood returning from the artificial kidney (through the venous-return cannula) was consistently and significantly greater than that of the blood entering the "kidney" from the arterial cutdown. The changes in hematocrit were neither great enough nor consistently in the proper direction to account for the increases in oxygen content. In addition, when the administration of oxygen to the patient via the tracheotomy was stopped, the arterial oxygen content decreased whereas the venous oxygen content remained essentially unchanged.* The constancy of the venous oxygen concentration under these circumstances is not surprising, for in passage through the

TABLE 2. *Arterial Blood Oxygen Content and Capacity.*

DAY	OXYGEN CONTENT	OXYGEN CAPACITY	SATURATION	HEMATOCRIT	COMMENT
	vol. per cent	*vol. per cent*	%	%	
12	4.78	10.85	44	26.0	
13	8.10	12.9	63	29.0	After 600 ml. of settled red cells
	6.24	13.2	47		Oxygen off for 3 min.
14	9.6	12.8	75	30.0	After 500 ml. of blood
	7.3		61		(Venous blood)
31	10.9	13.5	81	29.0	

120 feet of cellophane tubing, blood can equilibrate with the ambient gas under the hood of the machine which is a 90:10 per cent mixture of oxygen and carbon dioxide. As would be expected, there was no significant change in blood oxygen content during dialysis on the 21st day, when the patient's pulmonary complications were minimal and his arterial oxygen saturation was normal.

These studies showed that the oxygen content of the blood passing through the artificial kidney will invariably be increased if the oxygen content of the entering blood is less than normal. When the oxygen being administered to the patient was discontinued, the arterial oxygen content fell, and larger increases (5.0 to 7.0 vol. per cent) in oxygen content were observed. With a mean flow rate of 250 ml. per minute, this would deliver approximately 12 to 18 volumes of additional oxygen to the patient per minute. We suspect that the additional oxygenation accomplished during the second dialysis was in this order of magnitude, for sixteen to eighteen hours after that dialysis the arterial oxygen content was 4.78 vol. per cent despite the energetic therapy directed toward improving pulmonary function.

TABLE 3. *Changes in Blood Oxygen Content during Dialysis.*

DAY	DIALYSIS TIME	OXYGEN CONTENT	OXYGEN CAPACITY	SATURATION	HEMATOCRIT
	(hr.)	*vol. per cent*	*vol. per cent*	%	%
14	0.3	10.8	13.8	78	29.0*
		12.7	13.3	95	29.5†
	2.6	8.1	13.2	61	29.0*‡
		13.1		99	30.0†
17	0.2	12.4	14.4	86	32.0*
		14.2		99	31.0†
	3.5	13.5		91	33.0*
		14.3	14.8	97	33.0†
32	4.3	11.0	14.1	78	34.0*
		13.1		93	32.5†
	4.3	5.8		41	34.0*‡
		12.7		90	32.5†
21	0.2	11.8	11.8	100	27.0*
		11.3		96	25.5†
	3.2	12.6	13.3	95	28.0*
		12.7		95	28.0†

*Inflow to artificial kidney from radial artery.
†Outflow from artificial kidney to brachial vein.
‡Oxygen via tracheotomy tube turned off for 3 min.

In terms of total oxygenation the artificial kidney obviously does not compare with some of the modern pump oxygenators being used in cardiac surgery. However, in a patient with severe ventilatory impairment, the increased oxygenation that is accomplished during dialysis may be clinically significant. This appeared to be so in the case discussed.

SUMMARY

A case illustrating many of the problems encountered in the management of the oliguric patient is presented. An episode of prolonged hypoxia prompted studies demonstrating that the oxygen content of the blood may be increased in passage through the artificial kidney and that this will invariably occur if the oxygen saturation of the entering blood is less than normal. The implications of these findings in the present case are discussed.

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*In this laboratory differences in oxygen content must exceed 0.4 vol. per cent before they are regarded as significant.

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PREVENTION OF ASPIRATION OF GASTRIC CONTENTS DURING GENERAL ANESTHESIA*

SAMUEL GILMAN, M.D.,† AND ARTHUR L. ABRAMS, M.D.‡

BOSTON

ASPIRATION of gastric contents into the respiratory tract by the unconscious patient is a serious, and sometimes a fatal, hazard. In a series of 44,016 pregnancies studied at the New York Lying-in Hospital, Mendelson[1] reported 66 cases of aspiration of gastric contents into the pulmonary tree. Hingson and Hellman,[2] in 1951, analyzed 330 maternal deaths resulting from anesthesia and found aspiration of vomitus responsible for 155. The dangers of aspiration of stomach contents during general anesthesia have been documented by others.[3,4]

Although the hazard of aspiration of gastric contents from a stomach known to be full is well recognized, the hazard of aspiration from a stomach in the patient prepared for surgery is not well recognized. Culver and his associates[5] demonstrated that regurgitation occurred under general anesthesia in 26 per cent of 300 unselected patients prepared for surgery without food in the stomach, and 16 per cent aspirated gastric contents into the lungs. Silent aspiration occurred in 8 per cent. In a series of 926 patients prepared for surgery, Berson and Adriani[6] found that 14 per cent regurgitated gastric contents into the pharynx, and 7 per cent aspirated these contents into the trachea and bronchi. Similar findings reported by Weiss[7] emphasize the fact that the aspiration of gastric contents under general anesthesia may occur in the prepared patient, but the hazard is multiplied many times in the unprepared patient who has eaten before the induction of anesthesia.

The dangers of aspiration are more likely to be encountered under certain circumstances. First, and most apparent, are patients who have eaten just before surgery. The physiologic emptying time of the stomach is not a safe guide for assuming an empty stomach. Fatal aspiration of gastric contents fifteen hours after the last known meal has been reported. Any trauma, as well as the onset of labor, can delay by many hours the emptying time of the stomach. Secondly, patients with intestinal obstruction and distention are notorious risks for the induction of anesthesia because of the danger of sudden aspiration. The presence of an inlying Miller–Abbott tube in the upper intestinal tract does not ensure an empty stomach. Thirdly, patients suffering from severe acute conditions, such as peritonitis, intraperitoneal hemorrhage or wound rupture, may have marked gastric dilatation that becomes apparent when the patient loses consciousness. Fourthly, patients with massive upper gastrointestinal bleeding do not have their stomachs adequately drained by a Levin tube.

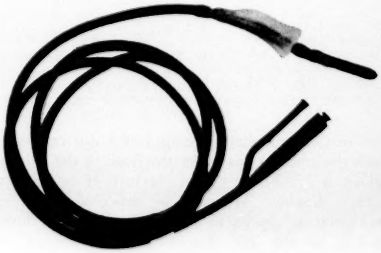

FIGURE 1. *Tube Described in the Text.*

Many methods have been used in the attempt to reduce the hazards of aspiration. Anesthesia by means of local and regional block, when practicable, successfully eliminates the hazard because a conscious patient can usually handle regurgitated material, even in large amounts. The purposeful induction of vomiting, either manually or by emetics, to empty the stomach before anesthesia may increase the hazard by establishing a hyperirritable vomiting reflex, which persists during anesthesia. The passage of an endotracheal tube with an inflatable cuff under topical anesthesia may be done before the induction of gen-

*From the Department of Anesthesia, Beth Israel Hospital.

†Clinical associate in anesthesia, Harvard Medical School; head of Anesthesia Department, Beth Israel Hospital.

‡Instructor in anesthesia, Harvard Medical School; associate in anesthesia, Beth Israel Hospital.

eral anesthesia. This method is satisfactory when the skill of the physician and the co-operation of the patient combine to allow passage of the tube; too often, however, this is not so. Reliance on a Levin tube is not safe because this tube cannot drain semisolid gastric contents. Our experience has shown that rapid, smooth induction of general anesthesia with Pentothal or cyclopropane is not a satisfactory method of prevention of aspiration of gastric contents in the presence of a full stomach. Since the hazard of aspiration is so great, it may be safer to defer the operative procedures until the following day. Therefore, the urgency of the operation in a patient with a full stomach must be assessed in terms of the risk of aspiration as well as in others.

It is possible to prevent the passage of liquid and solid materials from the stomach to the pharynx. In 1903 Kausch[9] suggested the use of a double-lumen gastric tube with an inflatable balloon to obstruct the cardioesophageal junction and thereby prevent the regurgitation of intestinal contents. This suggestion, made fifty-three years ago, has never found its way into general use. Macintosh,[10] in 1951, proposed that a gastric tube with an inflatable cuff be placed in the lower end of the esophagus to prevent distention of the stomach with anesthetic gases and the regurgitation of stomach contents in a thoroughly relaxed patient.

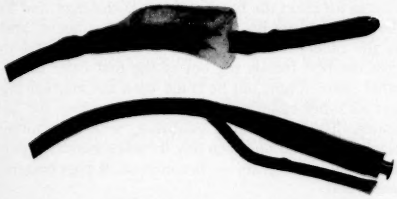

FIGURE 2. *Enlarged View of the Ends of the Tube.*

We have designed a double-lumen gastric tube with an inflatable balloon (Fig. 1 and 2) that has sufficient body to be passed easily through the nose into the stomach preoperatively.* The tube recommended is No. 16 Fr. and 122 cm. in length. The inflatable balloon is 5 cm. from the end. The tip has three perforations to drain the liquid and gaseous contents of the stomach. Once the tube is in the stomach, it is recommended that the balloon be inflated with 50 ml. of air. The tube is then withdrawn gently until slight resistance to further passage is felt. At that point the tube is securely fastened to the forehead by a circular 1-cm. adhesive strapping going completely around the circumference of the head. Then, general anesthesia is rapidly induced by any drug the anesthetist considers indicated in the given situation. For further protection a cuffed endotracheal tube may be inserted when the patient is sufficiently anesthetized.

This arrangement gives the physician a sense of security when he is inducing general anesthesia in a patient with a full stomach, and does not restrict him to the use of local or regional anesthesia. We have used this tube with general anesthesia in 5 cases of intestinal obstruction and marked gastric distention in which peripheral circulatory collapse contraindicated the use of spinal anesthesia. The tube was also used in a patient known to have ingested solid food two hours before the induction of general anesthesia. In none of these 5 patients was there any evidence of fluid or semisolid materials in the pharynx while the tube was in the stomach. It is recommended that the tube be left in place until the patient regains consciousness. The use of such a tube should reduce or eliminate the hazard of aspiration of gastric contents in the unconscious state.

*Manufactured by American Cystoscope Makers Incorporated, New York City.

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SPECIAL ARTICLE

SEARS-ROEBUCK FOUNDATION PLAN OF ASSISTANCE TO PHYSICIANS*

L. R. DAME, M.D.†

GREENFIELD, MASSACHUSETTS

NEVER before has the United States had so much superior medical talent. Simultaneously, however, at least three major trends have impaired the usual delivery of this talent to the sick in many areas. The first is the tremendous growth in the population accompanied by the ever-increasing movement to the suburbs with a fluidity comparable to the mass migrations westward in the 1800's. The people have really been moving away from their medical men and established medical facilities in many places. The second is that availability of physicians for replacement has been delayed, and the trend to early specialization somewhat accentuated, by the requirements of military service. The third is that physicians, on completion of their educational and military requirements, not only find their financial resources long since exhausted but also must meet the recent ever-increasing costs of assembling the equipment for modern practice in either rural or suburban locations, presenting an obstacle far different from that in the past.

This situation has been admirably described by Dr. George Lull, secretary of the American Medical Association as follows:

> The days when a physician could practice medicine from his little black bag and perform surgery on a kitchen table have long since passed. Today, the demands of the modern medical practice require that physicians have access to good medical facilities — offices in which the patient may receive the benefit of modern diagnostic techniques.
>
> Modern medical facilities enhance the potential services of each individual physician by providing him with a functional workshop in which to practice his profession.
>
> The many diagnostic tools of modern medicine call for a well-designed and functional medical office or unit. A physician who conducts his practice from a physical setup designed to meet his own and the community's needs can provide better medical service to his patients since he can make the best use of his own time and facilities.

To many people the name "Sears-Roebuck" produces a mental picture of a mail-order house, a huge catalogue, a few retail stores and nothing more. However, many years ago, this huge company realized that there must be not only a corporate body but a corporate soul as well, and it has been a leader with its principle that "Business must account for its stewardship not only on the balance sheets, but also in matters of social responsibility." In 1923 it established an agricultural foundation that was so successful that an enlarged foundation was later formed, and at last count over 4000 projects throughout all the states were being maintained in such fields as the Alaskan Floating Library, rural ministers' scholarships, nearly 16,000 agricultural scholarships and multiple farm-improvement plans. Also, lately a merit scholarship program has been established under which 100 four-year scholarships will be granted after nation-wide competition. Not only will the students be aided financially but also the colleges will be given an additional amount in unrestricted funds, in the realization that tuition does not meet all the expenses incurred in teaching students.

The central theme of all of these plans is to stimulate self-help and independence, reward industriousness and establish self-perpetuation of the plans if they prove worthy. This is best illustrated by one of the early plans, that of growing pigs. A two-month-old female pig would be given to each of about 10 boys in an area; the boys would raise the pigs, and to the boy with the best record would go a heifer, and to the others chickens. Each boy was obligated to give the best female pig out of the first litter to another selected boy, but he could keep the original pig and all other offspring. In a single county — for instance, Etowah County, Alabama, where in many places there had not been any livestock besides a dog and a mule for years — the original 8 pigs became over 7000.

In early 1955 the Sears-Roebuck Company conferred with the officers of the American Medical Association, and the "Plan of Assistance to Physicians Establishing Medical Practice Units" resulted. The plan is directed toward an important national need: the better distribution of medical care. It is based on the principle of self-help; it is not in any sense a give-away program. It has a feature of aid to the doctors themselves, but this is secondary to the primary purpose of encouraging physicians to settle in communities where their services are most urgently needed. This distinction should be well understood; most decidedly this is not just a plan to get doctors started in practice, but one to get them started where they can supply medical care not already available. All arrangements are confidential, and no community or physician is identifiable unless the physician thoughtlessly exposes himself.

The plan is very simple. The Sears-Roebuck Company will put into the plan $125,000 each year for

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†New England member, Medical Advisory Board, Sears-Roebuck Foundation.

ten years, will bear all the costs of investigation and maintenance and will fully co-operate in the administration of the plan. There is a Medical Advisory Board, which is composed of the President, President-Elect and Chairman of the Board of Trustees of the American Medical Association, and at least 2 physicians from each of the 5 major geographic divisions of the country. These members survey the medical needs of the proposed community and the qualifications of the physician applicants and make recommendations. These applications are acted upon in joint meeting of the Medical Advisory Board and the Sears-Roebuck Foundation directors, and these 30 representatives are extremely thoughtful.

Loans are granted in amounts up to $25,000 when funds are not available locally, are unsecured, cannot be used for outstanding debts and are for ten years. The money is to be used for medical equipment, instruments, remodeling of facilities, plans or new facilities, or anything else that will result in improved medical care. Repayments are to begin with the fourth year, but the borrower can start repayments earlier and finish earlier if he is able, thus saving himself interest and freeing the funds for others. There is a charge of $5 a month, payable monthly, on each $1,000 of principal; this charge is made not only because it is fair to do something in return for this aid but also to stimulate prompt repayment of the loan and put more aid into the fund for other communities and other physicians. Booklets portraying sample units, and application blanks, are obtainable from the main office of every state medical society, most of the medical schools and the headquarters of the American Medical Association in Chicago. Applications should be forwarded to the regional main office of the Sears-Roebuck Company, and all directions and addresses are given in the booklets.

These "medical units" may be a single physician establishing medical facilities in a rural or suburban area; such a unit was established in a mountain state in 1955. Or the unit may be the enlargement of existing facilities so that specialists' services can be provided at stated periods by certain physicians who travel in from a major center; such a unit was similarly established in 1955, when an unused second floor was remodeled. A medical unit may also be a new building for physicians in a community; one was in an area where a group of general practitioners were caring for patients in a garage 40 miles from a major center.

All the loans for 1955 were made to worthy communities and physicians, and the fund has already been further enlarged by the payments from borrowers and by the second-year grant from the Sears-Roebuck Company. The officials of the Sears-Roebuck Foundation and the Medical Advisory Board are highly pleased and stimulated by the ready acceptance of the central principles of the plan by the applying physicians and by their expressions of gratitude for this type of consideration.

Summary

This is a plan in which American medicine and American business enterprise co-operate as partners, to realize the principles of opportunity, incentive, mutual help and self-reliance; to give the American people the best possible medical care; and to help the American physician build for himself the most effective, the most rewarding and the most satisfying life as a professional man.

78 Federal Street

MEDICAL PROGRESS

NEUROLOGY (Continued)

WILLIAM K. JORDAN, M.D.,* AND H. HOUSTON MERRITT, M.D.†

LITTLE ROCK, ARKANSAS, AND NEW YORK, NEW YORK

DISEASES OF MUSCLE

Muscular Dystrophy

Four major types of biochemical abnormalities have been described in patients with muscle diseases.[33] These are as follows: creatinuria; alterations in muscle electrolyte metabolism, particularly potassium; pentosuria; and changes in serum aldolase and, less consistently, in serum phosphohexoisomerase and in several enzymes of muscle concerned with glycolysis and glycogenolysis. With the possible exception of the alterations in serum aldolase, it seems probable, at present, that all these changes are related to the reduction of functional muscle mass attendant upon muscular wasting, and do not reflect biochemical lesions specific for any of the currently recognized nosologic entities among the diseases of muscle.

*Professor of neurology, University of Arkansas Medical Center.

†Professor of neurology, Columbia University College of Physicians and Surgeons.

The problem of creatinuria has been reviewed recently by Milhorat.[34]

The "velocity of turnover"* of potassium in the whole body and the "index of potassium turnover"† in muscle biopsies of patients with muscular dystrophy have been determined by Shy et al.,[35,36] by means of radioactive-isotope-tracer technics. The former measure is lower in patients than in controls, but the latter falls within the same range in patients and controls. In other studies the potassium concentration in muscle biopsies from dystrophic patients is lower than that in controls, and the sodium concentration is higher, and evidence was obtained that dystrophic tissue contains fewer muscle fibers than does normal muscle tissue. The combination of lowered potassium concentration and reduced muscle mass contributes to the lowering of total body potassium content. These investigators consider their findings to indicate that the body of a dystrophic patient has a lower velocity of potassium turnover because it contains less potassium and not because the turnover in dystrophic muscle tissue itself is altered. They have concluded that the low potassium concentration in the muscles of patients with muscular dystrophy is not an etiologic factor in but, rather, a consequence of the disease. They believe, however, that the low potassium concentration may aggravate the disturbance of the muscle metabolism after the pathologic process has started.

Also using tracer technics, Rose and his associates[37] have measured the "exchangeable" sodium and potassium of the whole body in patients with muscular dystrophy or myotonia dystrophica and in members of the families of these patients. "Exchangeable" potassium was diminished in patients with muscular dystrophy and myotonia dystrophica. "Exchangeable" sodium was not significantly altered. Abnormally low "exchangeable" potassium was observed in 3 apparently healthy male siblings of patients with muscular dystrophy. A good correlation was observed among "exchangeable" potassium, creatinine excretion and physical disability in most patients with muscular dystrophy, but the correlation was poor in most of those with myotonia dystrophica.

Minot and her associates[38] reported several years ago that a pentosuria occurs in patients with muscular dystrophy, and identified this pentose as a ribose on the basis of its osazone derivative; subsequently, they presented evidence that the ribosuria did not accompany other diseases of muscle, nerve or spinal cord, and suggested that the test for ribosuria be used in the diagnosis of muscular dystrophy. In 89 cases of myopathy, Walton and Latner,[39] using the Minot method, found only 12 positive cases, and concluded that it was of no diagnostic value in myopathies. Drew and Selving[40] reported finding a pentosuria in both dystrophic patients and in those with other neurologic diseases. Ronzoni et al.[41] found no free ribose in paper chromatograms of urine from 20 dystrophic and 10 control patients, but observed ribose in most specimens after hydrolysis, presumably representing nucleotide-bound ribose. However, their results have been criticized on the basis of their method of treatment of the urine specimens before chromatography.[33] Smith and Matthews[42] have also reported failure to detect pentoses by chromatography of urine specimens from a small series of dystrophic patients.

Tower et al.[33] measured quantitatively the excretion of free pentoses (aldopentoses) in the urine of controls and of patients with various myopathies, including muscular dystrophy, myasthenia gravis, myotonia dystrophica and muscular atrophy (? causes) and identified these substances by paper chromatography (avoiding preheating of the specimens except for deionization). They found that on a per kilogram basis, the twenty-four-hour excretion of free pentoses by the myopathy group was approximately twice that of the controls. Semiquantitative estimation of type of pentose excreted suggested that in normal subjects arabinose predominated and in the myopathic group ribose predominated. The excretion of the pentoses correlated well with functional residual muscle mass as estimated by radioactive-potassium turnover, and the conclusion was drawn that the urinary excretion of pentoses, mostly as ribose, increases as the residual functional muscle mass is decreased in patients with the various myopathies studied.

Schapira and his associates[43] have reported an increase in serum aldolase in 72 of 77 patients with muscular dystrophy. The only other neuromuscular disease in which they have so far found an increase in activity of this enzyme was in a patient with myotonia dystrophica and in several patients early in the course of poliomyelitis. Less constant and less striking increases in phosphohexoisomerase were found in patients with muscular dystrophy. These investigators have also reported a decrease in aldolase, phosphorylase "a" and "b", phosphoglucomutase, and over-all glycogenolysis in muscle tissue from dystrophic patients, when the activities are referred to muscle noncollagenous nitrogen. These changes are not specific for muscular dystrophy, since they were also observed in atrophic muscle after nerve transection.

The occurrence of an inherited myopathy in mice, developing by mutation, has been described.[44] The histopathology of the myopathy resembles that of human muscular dystrophy. This strain of mice may provide a useful research tool, since it is apparently the first laboratory animal of known genetic background to present a myopathy similar to that found in the human muscular dystrophies.

*Velocity of turnover: microcuries of the dose minus microcuries excreted/microcuries of K_{42} per liter of urine divided by milliequivalents of K_{39} per liter of urine. (Urine collected over a twenty-two-hour period.)

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Myasthenia Gravis

According to present concepts and in simplified form the following successive events occur in normal transmission at the myoneural juncture: arrival of the nerve impulse at the juncture effects the release of bound acetylcholine; the acetylcholine, upon release, combines with specialized sites on the end-plate membrane-receptor surface; this combination results in a decrease in the transmembrane potential ("depolarization"), and a redistribution of ions across the membrane occurs, perhaps involving entry of sodium into the cell and egress of potassium; the muscle action potential ensues and invokes muscle contraction by an unknown mechanism; the bound acetylcholine is hydrolyzed by cholinesterase producing acetate and choline and the resting membrane potential is re-established; the muscle relaxes, and end plate and muscle fiber are in readiness to repeat the cycle.

Analysis of the mechanisms by which agents block neuromuscular transmission in normal subjects has led to the concept that some, such as decamethonium, induce a sustained depolarization of the end-plate region ("depolarizing block"), whereas others, such as tubocurarine, compete with acetylcholine for the specialized sites on the end-plate membrane surface ("competitive block").[45]

Recent experiments, based on these concepts, have led to a revision of the hypothesis that the essential defect in myasthenia gravis lies in a decreased sensitivity of the myasthenia end plate to acetylcholine.

As a result of a careful study of the effects of injection of acetylcholine, acetate, choline and other agents on neuromuscular transmission in normal subjects and in patients with myasthenia gravis, Grob, Johns and Harvey[46] have suggested that in myasthenia the events in neuromuscular transmission are normal through the stage of production of choline by hydrolysis of acetylcholine, but that the choline so released produces a competitive type of block in the myasthenia end-plate membrane, inhibiting the depolarizing action of acetylcholine released by subsequent nerve impulses. In normal persons choline was found to produce a predominantly depolarizing block, which Grob et al. consider to be less completely inhibitory of the depolarizing action of acetylcholine than the competitive block, and hence not associated with the myasthenic phenomenon.

They suggest that the difference in type of block produced by choline in normal subjects and in myasthenic patients may be due either to an abnormal response of the myasthenia end plate to choline or to the formation in myasthenic patients of an abnormal product of choline, which is a competitive blocking agent. It has also been found that decamethonium, which possesses a depolarizing block in normal persons, produces a competitive type of block in patients with myasthenia gravis.

When applied to myasthenia gravis the term crisis usually implies weakness of the muscles concerned with respiration or swallowing, or both, to such an extent that these functions cannot be maintained without mechanical aids.[47] It is now recognized that there are at least two types of crises in myasthenic patients[47]: "true" myasthenic crisis occurs in patients receiving either no or insufficient medication and in those who develop drug resistance; "cholinergic" crisis is the result of excessive medication. Occasionally, crisis is precipitated in patients with unsuspected myasthenia by administration of curarelike compounds for surgical and other purposes. Tether[47] has advised that whenever a myasthenic patient fails to clear secretions or to breathe adequately, tracheotomy or tracheal intubation, followed by tracheotomy, should be performed, thus assuring an airway through which oxygen can be given and secretions aspirated. A respirator should be used if voluntary breathing is inadequate. At this point, he states, an effort should be made to determine whether the crisis is on a myasthenic or a cholinergic basis, and recommends the following procedure: if excess secretion or miosis, or both, or relatively slow pulse is present, atropine, 1.3 mg., should be given intravenously. Atropine will alleviate the muscarinic symptoms of overdosage of the cholinergic agents, but will not relieve the weakness. If no improvement occurs with atropine, Tensilon, 2 mg., should be given intravenously, and the needle left in place. If improvement occurs, the crisis is probably myasthenic, and the patient will probably respond to increased dosages of cholinergic drugs. However, if muscle fasciculations occur, the crisis is probably cholinergic. If there is no effect within thirty seconds, an additional 8 mg. should be given. If muscle fasciculations and no improvement follow, cholinergic crisis should be suspected.

The search continues for more effective drugs in the therapy of myasthenia gravis. Neostigmine has long been the drug of choice, despite its three chief drawbacks, which are undesirable side effects such as gastrointestinal distress, relatively brief duration of action, particularly in severe myasthenia, and development of resistance to its effects. TEPP, OMPA, DFP and related drugs have not been found to be of general clinical use. Currently, attention is being paid to the use of Mestinon and Win 8077. Osserman[48] has reported that Mestinon is very effective in relief of myasthenic symptoms, and that although its action during the day is only slightly longer than that of neostigmine, it appears to have a longer action during the night, frequently permitting the patient a full night of sleep. He has found Mestinon to be definitely less toxic than neostigmine and believes that, because of the lesser danger of toxicity, it may be helpful in a patient resistant to neostigmine, but considers that as yet no drug or combination of drugs is effective when a patient is in a myasthenic crisis and resistant to neostigmine.

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Schwab[49] reported favorably on Win 8077 and has found that per milligram it is twice as active as neostigmine and that its duration of action is twice as long as is that of this drug.

Since the introduction of thymectomy in the treatment of myasthenia gravis by Blalock et al. in 1939, there has been much interest in this procedure here and abroad, and conflicting views of its efficacy have developed. Eaton and Clagett[50] have reviewed the experience at the Mayo Clinic in a large series of patients undergoing this procedure and have reviewed the world literature. They conclude that at present the evidence supports the opinion, at least in female myasthenic patients less than fifty years of age who do not have thymomas, that this operation is of value. This is essentially in agreement with the conclusion of Schwab and Leland.[51] They believe that the value of thymectomy in male patients and in females with thymomas has not been conclusively established as yet. Nevertheless, they recommend thymectomy for male patients as a potential benefit unless the risks of surgery contraindicate the performance of an operation, the worth of which is not yet conclusively established. X-ray therapy is reserved for those patients who are unsuited for surgical treatment. Eaton and Clagett believe that it is probably not wise to use thymectomy even in female patients if the disease has been present for ten years or more, particularly if it is stationary or improving.

The problem of the interrelations of pregnancy and myasthenia gravis has been discussed by Osserman.[52] He states that of 22 patients with myasthenia gravis, having a total of 33 pregnancies, 32 per cent showed a definite remission, 34 per cent showed no change in symptoms, and 34 per cent showed a definite relapse in association with pregnancy. The pattern of symptomatology was usually established during the first trimester, and only occasionally was there a change in the second and third trimesters. In patients with repeated pregnancies it was observed that each pregnancy had its own pattern of symptoms and did not necessarily follow the pattern of the previous one. Interruption of pregnancy in 6 severely ill patients did not affect the severity of the symptoms. In 7 cases there was spontaneous abortion, and this was accompanied by marked symptomatic improvement. Osserman states that labor and delivery were normal in all his patients, provided adequate cholinergic therapy was given, and he believes that the decision to do a cesarean section should be dictated by purely obstetric considerations. In 16 live births from this series there were 3 cases of acquired neonatal myasthenia gravis. The symptoms usually abated within the first few weeks of life. Cholinergic therapy may be required during the period of weakness.

Hepatolenticular Degeneration

Evidence has steadily accumulated during the past decade in support of the existence of at least two metabolic defects in hepatolenticular degeneration, or Wilson's disease. One of these defects involves copper metabolism. Brain and liver have increased copper contents,[53] urinary excretion of copper is increased,[53] total serum copper is usually low or normal,[54] and there is a deficit of the specific plasma copper-containing globulin, ceruloplasmin.[55] The second defect is in amino acid metabolism. There is an increased urinary excretion of amino acids with a normal serum alpha amino nitrogen level,[56] and several specific oligopeptides appear in the urine.[57]

Recent investigations have yielded more detailed information concerning these metabolic defects, and efforts have been made to relate them to one another, as well as to find a general explanation for this disorder.

With a chromatographic method based on use of the ion-exchange resin, Dowex-50, which permits accurate identification and measurement of amino acids, the amino acid distributions in the urine and in the plasma of patients with hepatolenticular degeneration were studied by Stein et al.[58] No qualitative or quantitative abnormalities in plasma amino acids were observed. Five of 6 patients exhibited abnormalities in urinary excretion of amino acids, whereas 1 had an almost normal excretion pattern. The highest levels of urinary excretion were observed in the cases of threonine and cystine (twenty times the normal value). Serine, glycine, asparagine, valine, tyrosine and lysine, and possibly glutamine, are excreted in five to ten times the normal amounts, and histidine, ornithine and phenylalanine in two to four times the normal quantities. Two amino acids not found in normal urine, proline and citrulline, appeared in considerable quantities in the urine of several patients. Aminoadipic and methionine, isoleucine, leucine and arginine tended to be least abnormal in their excretory levels, and on the average there appears to be a diminished excretion of taurine, 1-methyl histidine and 3-methyl histidine. Amino acids in conjugated linkages were found in the urine of patients with Wilson's disease in quantities about double those obtained from normal urine. In normal persons qualitative and quantitative aspects of amino acid excretion were found to be relatively insensitive to the amount of protein in the diet. However, patients with Wilson's disease manifest a marked sensitivity to protein intake concerning the level and pattern of amino acid excretion. These investigators agree with the previous conclusion that the aminoaciduria in hepatolenticular degeneration is the result of a renal lesion. They point out that, although some of their findings are compatible with a "lowered renal threshold" for amino acids in this disease, several features of their observations cannot be readily explained in this manner — for example, the lower than normal excretion of taurine and the methyl histidines found in some cases.

Normally, about 96 per cent of the serum copper is bound by the alpha-2 globulin, ceruloplasmin, which does not react directly with sodium diethyldithiocarbamate; the remainder of serum copper is capable of direct reaction with this reagent, and is probably loosely bound to serum albumin.[54] Cartwright et al.[54] have shown that although the total serum copper is reduced in Wilson's disease, the direct-reacting serum copper is significantly increased above the normal (a mean value in their series of 26 microgm. per 100 ml. in patients with Wilson's disease as compared with the normal value of 8 microgm. per 100 ml.).

Recently, Scheinberg[59] has shown that the hypercupremia of pregnancy and the hypocupremia of the newborn are related to an excess and deficiency, respectively, of ceruloplasmin.

Bearn and Kunkel[60] have observed that after administration of radioactive copper by mouth to normal persons or to patients with cirrhosis of the liver (in whom an increased ceruloplasmin may be present) there is an immediate uptake of copper by the serum albumin fraction. The radioactive copper shifts within a few hours to the ceruloplasmin. However, when radioactive copper was administered to patients with Wilson's disease, the copper was confined to the albumin fraction, and little or no shift occurred to this ceruloplasmin fraction. They suggest that since copper is first associated with the albumin fraction after absorption from the intestine, it is likely that this fraction is concerned with the transport of copper to various tissue copper proteins and to ceruloplasmin. The reduction in total serum copper occurring in most patients and the failure of a shift to ceruloplasmin of ingested copper in patients with Wilson's disease are apparently related to the deficiency of ceruloplasmin in this condition.

Cartwright et al.[54] have found that in 6 patients with Wilson's disease the spinal-fluid copper concentration was three times that in a control group of 11 patients, and that all the copper in the spinal fluid was of the direct-reacting type in the cases of hepatolenticular degeneration, but in the control group only half the copper was of the direct-reacting variety.

Cartwright and his associates[54] studied copper balance in 4 patients with Wilson's disease, 3 normal persons and 2 patients with active rheumatoid arthritis. In the normal subjects intake and output were essentially the same. The patients with Wilson's disease were in positive balance to the extent of about 0.56 mg. of copper per day of copper ingested, and the patients with active rheumatoid arthritis were also in positive copper balance.

After the oral administration of radioactive copper to 2 patients with Wilson's disease, Matthews[61] found that the plasma radioactive levels were slightly higher than those of controls, that a larger portion of the administered radioactive copper was excreted in the urine of the patients than of the controls, and that a larger percentage of the copper was found in the feces of controls than of patients.

Whether the positive copper balance in Wilson's disease is a result of increased absorption or diminished fecal excretion of copper is not clear. The observation of diminished fecal copper excretion makes it difficult to eliminate the possibility that the positive balance is the result of diminution in fecal excretion.[54]

Considerable evidence has been obtained suggesting a correlation between copper and amino acid urinary excretion in Wilson's disease, at least under special conditions.[54] Increased protein uptake and administration of cortisone in these patients induce a prompt and parallel rise in urinary copper and amino acid excretion[62]; also, intravenous administration of casein hydrolysate provokes an increase in urinary copper excretion.[54] Large doses of glycine and alanine are reported to increase urinary excretion of copper in this condition.[63] However, Uzman[64] found, in his study of a single patient with massive aminoaciduria and an increased copper excretion, that in the "resting" state (no agents administered), the daily output of copper bore no relation to the aminoaciduria. He has adduced evidence that the copper found in the urine of patients with Wilson's disease in the "resting" state is present mainly as a complex with the urinary peptides of a specific structure, mainly those having dicarboxylic amino acids as terminal residue, which he previously described as being in the urine in this condition.

In the "resting" state, approximately 58 per cent of the urinary copper of patients with Wilson's disease is dialyzable. Administration of casein hydrolysate increases the total urinary excretion of copper, as stated previously, but the percentage of dialyzable copper remains the same. On the other hand, in the increased cupriuria induced by BAL and intravenous administration of calcium versenate, the urinary dialyzable copper rises to approximately 80 per cent. In doses so far used, Versene by mouth does not appreciably increase urinary copper excretion.[54]

At present two conflicting hypotheses concerning the biochemical mechanisms of this disorder are entertained. According to one theory the disturbance in copper metabolism is primary; according to the other the disturbance in amino acid metabolism is basic.

One theory[62] holds that there is an increase in copper absorption, leading to an accumulation of copper in the tissues, producing the Kayser–Fleischer ring in the cornea, and the brain and liver disorders. Aminoaciduria and peptiduria are held, by this theory, to be the result of a functional impairment of the kidneys secondary to copper accumulation. The increased excretion of copper is thus related to the

increased excretion of amino acids secondary to the aminoaciduria. The other theory[64] holds that there is a disorder in protein synthesis or breakdown, leading to the accumulation of abnormal peptide residues in cells, which in turn bind copper. These copper-containing oligopeptides are released into the blood, and the aminoaciduria is thought to be the result of competition for absorption in the kidney tubules between these peptides and the amino acids, with preferential (but not complete) absorption of the oligopeptides leading to the massive aminoaciduria, and an excretion of some of the oligopeptides.

On the basis of their observations of the magnitude of the positive copper balance of patients with Wilson's disease, and of the effect of various agents on this positive balance, Cartwright et al.[54] have made some valuable therapeutic suggestions. They point out that patients with Wilson's disease may be in positive copper balance to the extent of 0.50 to 2.5 mg. of copper a day. The chelating agents that they use mobilize about 0.5 to 1 mg. of copper a day. In at least 1 of their patients, the chelating agents did not establish positive copper balance. They find that as soon as the agent is stopped, the positive copper balance is re-established. They point out that in view of these facts it is more surprising that a few of the patients show improvement rather than that all are not benefited. They suggest that therapy (with the available agents) be more energetic and more continuous, and that more effective agents be found. They suggest the following schedule of therapy for patients with Wilson's disease: the patient should be given a high-protein diet, thus promoting an aminoaciduria, which will increase excretion of copper in the urine; also, he should be given 20 mg. of potassium sulfide with each meal to decrease the absorption of copper. They recommend five-day courses of BAL (2.5 mg. per kilogram of body weight twice daily) or casein hydrolysate (1 liter of 5 per cent solution a day), to be given every ten days until maximum improvement occurs. Ideally, they believe that this regimen should be maintained continuously.

Recent observations of Walshe[65] on the effectiveness of penicillamine by mouth in promoting copper excretion in patients with Wilson's disease may make the meeting of criteria of Cartwright et al. for continuous therapy more possible. Repeated injections of BAL are painful and often associated with undesirable side reactions. It has been observed that beta, beta-dimethylcysteine (penicillamine) is excreted in the urine in the reduced (SH) state after administration of penicillin. On the basis of this observation Walshe hypothesized that this material would remain reduced if administered orally, and that the thio group might be active in the removal of copper from the body. He administered penicillamine to 2 patients with Wilson's disease and found that it was as effective as BAL when equal molecular amounts of sulfur were given, producing an increase in copper excretion in these patients. No toxic reactions were observed in short-term experiments.

(To be concluded)

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MEDICAL INTELLIGENCE

HIATUS HERNIA IN PREGNANCY*

ARTHUR C. GORBACH, M.D.,† AND
DUNCAN E. REID, M.D.‡

BOSTON

DIAPHRAGMATIC hernias have been diagnosed with increasing frequency in the past twenty years because more frequent x-ray studies are made of the upper gastrointestinal tract. These hernias may be responsible for a variety of symptoms referable to the gastrointestinal or cardiorespiratory system. In general, they tend to occur in older age groups, and are somewhat more frequent in women.[1] The role of pregnancy in the development of diaphragmatic hernia has not been determined. Since increased intra-abdominal pressure is thought to be one of the predisposing factors, it is not unlikely that this lesion occurs during pregnancy and is responsible for some of the disturbing gastrointestinal symptoms during gestation.

The following cases of diaphragmatic hernia complicating pregnancy were recently observed at the Boston Lying-in Hospital.

CASE REPORTS

CASE 1 (B. L. H. 50687). A 45-year-old gravida 4, para 3, was admitted to a general hospital at 36 weeks of gestation because of an episode of massive hematemesis. The hemoglobin on admission was 5.5 gm. per 100 ml. The prenatal course had been uncomplicated until 3 months previously, when almost daily vomiting and substernal pain relieved by sitting up developed. Similar complaints had not been noted in previous pregnancies. A gastrointestinal series showed a large hiatus hernia with a filling defect, thought to be possibly malignant. Cancer was ruled out by gastroscopy and biopsy. The patient was transferred to the Boston Lying-in Hospital and treated with a bland diet, antacids and elevation of the head of the bed. No further hematemesis occurred, and symptoms were relieved. After 5 days she went into labor, and delivery was easily accomplished. Post partum, she was symptomatically relieved, but her stools were persistently guaiac positive. X-ray study showed little change in the size of the hernia. She was referred back to the general hospital, where a successful surgical repair was done two months after delivery because of a recurrence of substernal pain.

CASE 2 (B. L. H. 183164). A 29-year-old gravida 3, para 2, a highly emotional patient, was admitted to the hospital during the 2d month of pregnancy because of persistent, severe nausea and vomiting. X-ray study of the upper gastrointestinal tract showed a large hiatus hernia. She was temporarily relieved by symptomatic therapy, but was readmitted to the hospital during the 5th month with severe nausea and vomiting of undigested food, together with substernal pressure and discomfort and failure to gain weight. Surgical correction was considered, but she improved rapidly on bed rest, antispasmotics and antacids, and was discharged from the hospital 9 days later. Symptoms were fairly well controlled on this regimen for the remainder of pregnancy. She went into labor at term, and delivery was carried out without difficulty. Post partum, she was completely relieved of gastrointestinal complaints.

These 2 cases illustrate the variable clinical picture associated with esophageal hiatus hernia in pregnancy. Because of them a study was undertaken at the Boston Lying-in Hospital to determine the frequency with which hiatus hernia is the cause of gastrointestinal complaints during the latter part of pregnancy.

REVIEW OF THE LITERATURE

A review of the literature reveals two distinct clinical forms of diaphragmatic hernias associated with pregnancy. A small number of severe cases have been reported[2-9] in patients who, during labor or shortly after delivery, become acutely ill with left-sided epigastric pain, vomiting, and various degrees of shock, with or without cyanosis and dyspnea. On physical examination, peristaltic sounds are heard in the left hemithorax, with a shift of the heart and mediastinum to the right. There is herniation of the stomach and sometimes the transverse colon into the left hemithorax, with strangulation of the involved portion of the gastrointestinal tract. Most of these patients have died promptly, and autopsy has shown a large opening in the left leaf of the diaphragm, the so-called pleuroperitoneal hiatus or foramen of Bochdalek. A few of these patients have been promptly operated on and have recovered.[10,11] Fortunately, this type of diaphragmatic hernia is rare.

A more common type seen in pregnancy is the esophageal hiatus hernia,[12-17] in which, owing to a congenitally short esophagus or an enlarged normal esophageal opening, the upper part of the stomach is found above the diaphragm. These patients may fail to improve from the usual morning sickness of early pregnancy, and may be thought to be suffering from hyperemesis or psychiatric disorders, more specifically hysteria.[18] About the twentieth to the thirtieth week of gestation intractable heartburn develops and tends to become more severe as pregnancy progresses. The patients may also complain of indigestion, regurgitation, loss of weight and hematemesis. By the third or fourth day after delivery, the patient is usually completely relieved of all gastrointestinal distress.

The question of how much clinical significance can be placed on hiatus hernias discovered on x-ray study and how often asymptomatic hernias occur has never been accurately established. Some authors believe that a fourth to a fifth of all hiatus hernias are

*From the Department of Obstetrics, Harvard Medical School, and the Boston Lying-in Hospital.

†Instructor in obstetrics, Harvard Medical School; assistant obstetrician to outpatients, Boston Lying-in Hospital.

‡William Lambert Richardson Professor of Obstetrics, Harvard Medical School; obstetrician-in-chief, Boston Lying-in Hospital.

asymptomatic, and others place the figure much lower. Brick and Amory[19] performed x-ray examinations on 500 persons over fifty years of age without symptoms, who, because of their age, would be expected to have a relatively high incidence of hiatus hernias. However, these authors found only 4 cases, and they conclude that asymptomatic hiatus hernias are uncommon.[19] Hiatus hernias in pregnancy appear to be significantly frequent. Ringler and Eneboe,[20] in an x-ray study of 195 women in pregnancy, found the lesion in 18 per cent of multiparas, and 5 per cent of primiparas. They made no attempt to correlate the x-ray and clinical findings, but stated that many of their patients "had the usual gastro-intestinal symptoms" of pregnancy.

Material and Methods

This study from the Boston Lying-in Hospital was undertaken to determine the relative frequency of esophageal hiatus hernia as a cause of persistent gastrointestinal symptoms during pregnancy. Fifty patients from the prenatal clinic who presented such complaints as heartburn, nausea and vomiting, or hematemesis in the latter part of pregnancy, were screened for the presence of esophageal hiatus hernia by means of a simple barium swallow and fluoroscopy. A complete upper gastrointestinal series was not performed, but care was taken to demonstrate the hernia during x-ray examination and fluoroscopy since the lesion may be easily overlooked. The position of the patient is particularly important in this regard, for many hernias are not seen in the upright position but are easily demonstrated when the patient is horizontal.

This study was conducted over a twenty-six-month period, during which there were 5146 live births in the clinic. By no means all the clinic patients with persistent gastrointestinal symptoms in the latter part of pregnancy were given x-ray examinations during this period when the study was conducted. The group of patients studied tended to be those with more severe symptoms, who were co-operative and willing to submit to the examination. A large number of clinic patients with gastrointestinal complaints during this twenty-six-month period were not examined roentgenologically.

Results

Of 50 patients screened for the presence of esophageal hiatus hernia 31, or 62 per cent, demonstrated this lesion. On x-ray examination the hernias varied from small nubbins to large hernias estimated to be 9 cm. in diameter. There appeared to be no correlation between the size of the hernia and the severity of clinical symptoms. In patients who did not have a demonstrable hiatus hernia, there was no other abnormality on x-ray examination to explain the gastrointestinal symptoms.

This study helps to explain the significance of heartburn during pregnancy. Of 31 patients with proved hiatus hernias during pregnancy 28, or 90 per cent, complained of heartburn that followed a definite clinical pattern. The heartburn was noted thirty to sixty minutes after a full meal or was initiated or aggravated by lying down. Antacids afforded some relief in some cases, and most patients were helped by standing or sleeping with the head elevated. A few were improved by vomiting.

Eleven, or 58 per cent, of the 19 patients with negative x-ray examinations also complained of heartburn, but in these patients, the heartburn did not tend to bear such a close relation to eating or recumbency as in those with a demonstrable hiatus hernia. It appears, therefore, that this lesion is a major but not the sole cause of heartburn in the latter part of pregnancy. A carefully taken history may contribute to the identification of patients with hiatus hernias.

The patient's age had no great effect on the development of hiatus hernia during pregnancy, the average age in the 31 proved cases being twenty-eight and nine-tenths years. This condition is definitely more common in multiparas, for 24 of the 31 patients had borne children. In nonpregnant persons, severe degrees of anemia frequently accompany hiatus hernia. This was not found in these 31 pregnant women. The hemoglobin levels were all above 10.5 gm. per 100 ml.

Treatment is largely symptomatic. Measures found to be most effective are elevation of the head of the bed and frequent, small feedings of a bland diet. Antacids and antispasmotics are not particularly helpful. Delivery has been carried out without incident, and it has not been necessary to terminate pregnancy prematurely or to perform cesarean section because of the hiatus hernia.

Even though this group has not been studied for a long period after delivery, it is believed that patients with a hiatus hernia during pregnancy should have a careful and prolonged follow-up study. Sprafka et al.[21] have followed a group of nonpregnant patients with hiatus hernias up to six years, and have found that about 20 per cent of small hernias progress to large hernias and that complications develop in about 30 per cent of patients with large hernias. Most authors agree that surgical treatment should be reserved for complications (ulceration, stricture formation or severe pain).

Summary and Conclusions

Sixty-two per cent of patients with persistent gastrointestinal symptoms in the latter part of pregnancy were found to have hiatus hernias.

Hiatus hernia is a frequent but not the sole cause of heartburn in the last half of pregnancy. X-ray examination should be performed on patients with persistent gastrointestinal symptoms in the last half of pregnancy, with special efforts to demonstrate a hiatus hernia.

Treatment is symptomatic during pregnancy. There is little effect on the eventual outcome of pregnancy with hiatus hernias.

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PROTEINURIA AND HYPOTHYROIDISM*

THOMAS J. ROESS, M.D.,† AND RICHARD P. LEVY, M.D.‡

CLEVELAND, OHIO

SINCE both hypothyroidism and renal disease may have in common the findings of periorbital edema, lassitude, weakness and anemia, it is of some interest to know whether albuminuria is also encountered in both disorders. Although current textbooks of medicine seem unanimous in stating that albuminuria may often be found in hypothyroidism[1-5] a careful review of the literature does not definitely substantiate this.

The description of hypothyroidism by Sir William Gull in 1873 reported the urine as normal in the 2 cases described.[6] In Murray's review of the life history of the first myxedematous patient treated with thyroid, as quoted by Major,[6] it is stated specifically that the urine contained no albumin before treatment. In 1927 Lawrence[7] studied 30 cases of hypothyroidism with low basal metabolic rates and 10 cases of frank myxedema. He found that 3 of the myxedematous patients and 4 of those with nonmyxedematous hypothyroidism had albuminuria. A significant number of the patients in this series had glycosuria or hypertension or both. It is not specified whether the patients with albuminuria were also those with the concomitant abnormalities, which are also potential causes of albuminuria. In 1928 Lawrence and Rowe[8] commented on "the high incidence of small amounts of albumin" in the urine of people with thyroid disease. They listed 126 hypothyroid patients, of whom 29 per cent were said to have had albuminuria. These workers, however, did not mention whether any of these patients had associated conditions that are known to cause albuminuria, or whether the albuminuria cleared with replacement therapy. MacKay and Sherrill[9] found that in hypothyroidism there was a correlation between the decrease in basal metabolic rate and exogenous urea clearance, but no data on the frequency of albuminuria was presented. Beaumont and Robertson[10] also studied renal function in myxedema. In 6 of 7 myxedematous patients urea clearances were low, and subsequently improved with replacement therapy. Albuminuria was not found in any case. Two patients with myxedema studied by Corcoran and Page[11] showed reduction of renal blood flow, glomerular filtration and tubular secretory capacity, which reverted toward normal with treatment. These workers did not comment on the presence or absence of proteinuria.

Thus, the available data on the association of albuminuria and hypothyroidism do not exclude the possibility that proteinuria, when seen in this condition, is due to an unrelated associated disease.

Clinical Material and Results

To evaluate this problem further, the hospital records of all patients discharged from either the private or staff medical services of the University Hospitals of Cleveland between January, 1952, and December, 1955, were reviewed. Although the diagnosis of hypothyroidism had been made on 120 such patients, only 15 were found who fulfilled the following criteria: unequivocal clinical findings of full-blown hypothyroidism; at least two of the commonly accepted laboratory results characteristic of hypothyroidism — namely, basal metabolic rate below −20 per cent, serum cholesterol above 350 mg. per 100 ml.[12] or twenty-four-hour thyroid uptake of a tracer dose of I^{131} below 8 per cent; and no thyroid substitution therapy instituted before diagnostic investigation and at least two urinalyses were performed. This group was composed of 11 females and 4 males, ranging in age from fifteen to seventy-six years.

Only 1 patient did not entirely fulfill the criteria

*From the departments of Medicine, Western Reserve University School of Medicine and University Hospitals of Cleveland.

†Formerly, senior assistant resident in medicine, University Hospitals of Cleveland.

‡Instructor in medicine, assistant attending physician and director of Health Service, University Hospitals of Cleveland.

listed above. However, the clinical picture, the therapeutic response to desiccated thyroid and 1.3 per cent twenty-four-hour I^{131} uptake by the thyroid gland left no doubt of the diagnosis of myxedema. Of the group, 3 patients showed persistent, and 2 transient proteinuria. The first of the 3 patients with persistent proteinuria also had well documented arteriosclerotic heart disease, and her usual blood pressure was approximately 180 systolic, 90 diastolic. The second patient also had considerable albuminuria at the time hypothyroidism was detected. However, this patient was known to have had hypertensive cardiovascular disease, with blood pressures in the range of 170 systolic, 115 diastolic; in this case the albuminuria persisted unchanged even after she was maintained on adequate thyroid therapy. Before thyroid therapy, the third patient showed a + test for albumin on four urine specimens and + + + on one, and no albumin on another occasion. During the first two and a half weeks after institution of thyroid therapy, five urine specimens gave a + test for albumin, and two were albumin free. She was readmitted to the hospital eighteen months later, euthyroid on adequate maintenance therapy; the urine was albumin free on the two determinations performed. The third patient also had hypertensive cardiovascular disease, with blood pressures ranging from 182 systolic, 120 diastolic, to 140 systolic, 85 diastolic. The 2 patients with transient proteinuria showed + and + + tests for albumin on initial urinalysis but were albumin free on at least two subsequent urinalyses done before any thyroid medication was begun; the former had hypertensive cardiovascular disease, and the latter chronic pyelonephritis.

Discussion

Although the high protein content of the transudates of myxedema and the demonstration of impaired renal function in this disorder might lead to the logical assumption the proteinuria would be frequently encountered, the data presented do not confirm this hypothesis. Of the 15 untreated patients studied, 10 failed to show albuminuria. The 5 remaining patients who did have proteinuria were found to have coexisting disorders that in themselves could adequately have explained the albuminuria. In only 1 of these cases did the facts suggest that clearing of proteinuria might have occurred on thyroid replacement therapy.

Summary and Conclusions

The frequency of albuminuria as one of the findings in hypothyroidism is discussed.

Of the 15 cases of proved hypothyroidism reviewed, only 3 showed persistent proteinuria. Each of these had associated significant vascular disease, and none showed unequivocal clearing of the albuminuria on thyroid therapy.

These data suggest that albuminuria may not occur in uncomplicated hypothyroidism.

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CURRENT CONCEPTS IN THERAPY*

Sedative-Hypnotic Drugs. I.

THE questions of when to use, which to use and what may be accomplished from sedative-hypnotic drugs are, at times, very perplexing. The recent introduction into therapy of several new groups of these drugs and the confusion created by the new central depressants with limited or no hypnotic action has made the problem even more difficult. Certainly, there is a wide variety of agents from which to select. It is therefore becoming increasingly important that the proper drug be employed if satisfactory results are to be obtained. Since there are so many sedative-hypnotic drugs it is necessary to group them according to the sedation problem presented. In general, sedative drugs are used far too often and frequently serve as poor, temporary and at times not so temporary substitutes for more definitive therapy. The decision to use them should not be made lightly since they are seldom a means in themselves. Only after careful evaluation of the patient and with a thorough understanding of what the drugs can and cannot do should such therapy be undertaken.

These drugs are of considerable value in numerous situations. The principal ones include sudden stressful situations, insomnia, hypertension in which sedation is desirable until the patient has learned to lead a more relaxed existence, pain to potentiate analgesic drugs, the control of convulsions, suppression of epileptic attacks, promotion of amnesia in obstetrics, sedation of patients before and after operation to create

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anesthesia and, finally, in narcoanalysis or narcotherapy.

The chief problems concerning them and certainly the most widespread use and demand for their action arise in stressful situations and in insomnia. Their use in the remaining situations is more limited and better controlled, and presents much less basis for confusion and difficulty. Therefore, their employment in stress and insomnia is of most concern.

Stressful situations may arise at any time and can be short and self-limited or prolonged and, at times, beyond the control of the patient. The short, self-limited situation is usually handled well by almost any of the potent sedatives. The prolonged state is more serious and requires skillful handling if difficulties are to be avoided. In this condition the drugs should be selected carefully and used only in conjunction with other more definitive therapy. Effective long-acting agents of low toxicity, low addiction propensity and low cost should be selected. Every effort must be made to reduce the dose and discontinue the drug as soon as the patient is able to adjust properly. The drug selected should be the one best suited to the individual case: sometimes one, and sometimes another, proves best. In recent years it is becoming more apparent that long-continued stressful situations are frequently helped considerably by the central-nervous-system depressants that have only a limited sedative effect.

Insomnia may be produced by a variety of conditions and appears in various patterns.* Frequently sedative-hypnotic agents are most useful in insomnia until the basic cause is found and eliminated. Most satisfactory control is obtained when the proper drug for the particular insomnia pattern is administered. Most patients with insomnia fall into one of four groups. The first includes those who become more and more tense as the day develops, until by bedtime they are in a high state of tension and unable to relax; when they go to bed they are unable to sleep, and toss and turn and resist sleep for an hour or two or more before they sink into a deep sleep of exhaustion. Usually, they find it is hard to arise in the morning. The majority of patients in this group are young, active persons or those exposed to a sudden stressful situation. A quick-acting, rapidly dissipated drug given in a hypnotic dose is desirable for these patients.

Secondly, there are persons who are nearly the opposite of the first group. These patients become more and more fatigued during the day and by evening are so sleepy that they have difficulty keeping awake. They readily fall asleep in their chairs after the evening meal and can hardly wait to get to bed. Once in bed they promptly sink into a deep sleep, only to awaken earlier and earlier in the morning, usually beginning at 5 and then 4 and even 3 o'clock, after which they have difficulty returning to sleep. Frequently, they get up, wander about, take nourishment, read or begin some daytime activity. In other words, they are gradually turning night into day. Most of these are older patients who frequently have considerable arteriosclerotic changes. A smaller percentage are under continued stressful situations that have created anxiety, worry and mental fatigue. They are exhausted by the day's stress, but awaken early in the morning and begin to worry or consider their problems. A slow, long-acting, mild sedative is usually most satisfactory for these patients.

The third group consists of persons who fall asleep readily when they retire but awaken after a period of one or two hours, and then after a brief period of being awake, fall back to sleep again and repeat this pattern four or five times a night. These patients have intermittent insomnia. Frequently, the insomnia is created by a low-grade fever producing night sweats, hyperactive vasomotor activity as in the menopause, with hot flashes and sweating, or a diseased joint, tendon, muscle or other structure that is subjected to painful stimuli during sleep when the usual protective splinting or shielding is relaxed. Older patients with poor circulation who have leg cramps or are restless because of leg aches also belong in this group. A moderately long-acting, highly potent hypnotic frequently given in conjunction with an analgesic drug or quinine is most helpful for such patients.

Finally, the fourth group comprises persons who honestly believe they have had no sleep in weeks or months. They are certain that they are wide awake all night since they have heard the clock strike all the hours and are continually aware of everything that happens throughout the night. This continual loss of sleep worries them, and they are convinced that something is wrong and that they will ruin their health. Usually these patients are tense, anxious persons in good physical health. It is apparent that they are receiving adequate rest, or they would be in a more serious physical state. Generally, they sleep lightly and flutter in and out of sleep rapidly. The moments when they are asleep are, of course, not registered consciously whereas the frequent periods during which they are awake are registered and seem to them to be a continuous flow. Actually, they are probably receiving nearly an adequate amount of sleep. However, agents that deepen their sleep pattern and prevent the rapid fluctuations are desirable and frequently afford considerable relief. Usually, a mild, long-acting preparation is most effective in this situation.

There are so many sedative-hypnotic drugs and central-nervous-system depressants now available that it is necessary to consider them in groups and indicate when each finds its most effective use.

This discussion will be continued in next month's column.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42371

PRESENTATION OF CASE

A seventy-year-old man was admitted to the hospital because of "indigestion."

About twenty-four hours previously he began to have "indigestion" with nausea and one or two minor episodes of vomiting. There was no hematemesis or diarrhea. These symptoms occurred two hours after a meal of soup and old fried fish. Midsternal tightness as well as palpitation were also noted. There was no sweating or faintness. From the onset of symptoms until the time of admission he was markedly anorectic. During the day before admission he had nothing to eat or drink; he was oliguric and had a normal bowel movement.

For five years he had had known diabetes mellitus that was controlled by diet. The day before admission the urine gave an orange test for sugar, and on the day of admission it gave a green test. An incarcerated inguinal hernia had been present for many years without associated symptoms. A suprapubic cystostomy was performed ten years previously because of urinary retention.

Physical examination showed a lethargic, markedly dehydrated man who vomited several times. The heart was not enlarged. The cardiac sounds were distant, and the rhythm was irregular. Examination of the abdomen showed no tenderness or distention. Peristaltic sounds were infrequent. The liver, which was nontender, was palpable 3 fingerbreadths below the right costal margin. The upper border of liver dullness was low. The spleen was not felt. A large, incarcerated, nontender inguinal hernia was present on the left. Rectal examination showed slight prostatic enlargement, without tenderness or induration. Neurologic examination was negative.

The temperature was 100°F., the pulse 90 to 150, and the respirations 18. The blood pressure was 90 systolic, 78 diastolic.

The urine gave a +++ test for albumin, a green test for sugar and a +++ test for acetone; the sediment contained an occasional granular cast and a rare white cell per high-power field; a culture was negative. Examination of the blood revealed a hemoglobin of 15.2 gm. per 100 ml. and a white-cell count of 13,700. The serum nonprotein nitrogen was 75 mg., the iron 70 microgm., the uric acid 6.9 mg., and the fasting blood sugar 410 mg. per 100 ml. The serum potassium was 5.2 milliequiv., and the carbon dioxide 25 milliequiv. per liter. The amylase was 14 Russell units. An x-ray film of the abdomen demonstrated a number of dilated loops of small intestine in the left flank having the appearance of jejunum; several loops of gas-filled intestine were seen in the inguinal hernia; the colon contained scattered gas and fecal material. Films of the chest showed a questionable small area of infiltration at the right-lung base. An electrocardiogram showed a supraventricular rhythm at a rate of 177 with periods of normal sinus rhythm at a rate of 100; the QRS interval was 0.08 second; the axis was −80°; QR waves were present in Leads aVR and V_2R; there were RR′ waves, with elevation of the ST segments and inversion of the T waves, in Leads V_1 and V_2.

The patient remained hypotensive and oliguric and took very little fluid orally. About fourteen hours after admission there was a sudden onset of abdominal cramps and distention, with associated substernal tightness, pulmonary edema and cyanosis. He became disoriented and then comatose, with an unobtainable blood pressure. There was no distention of the veins of the neck. Peristaltic sounds were absent. The temperature was 103.2°F. A blood culture was negative. An electrocardiogram showed a sinus tachycardia at a rate of 131; the PR and QRS intervals were 0.16 and 0.08 seconds, respectively; the axis was −85°; QR waves and elevated ST segments were present in Leads VR, V_1 and V_2; RR′ waves, with elevation of the ST segments, were present in Lead 3; an RS pattern, with upright T waves, was present in Leads V_4 through V_6. With oxygen, intravenous infusion of fluids, Levophed and 1800 ml. of plasma the pulmonary edema subsided, the color improved, the blood pressure was maintained at 100 systolic, and he became slightly responsive and no longer complained of abdominal pain. Four hours later an electrocardiogram showed a sinus tachycardia at a rate of 125; the PR and QRS intervals were 0.16 and 0.08 seconds, respectively; the axis was −85°; there were QR waves in Lead VR; RR′ waves were present in Lead V_1; the ST segments were elevated in Leads V_1 through V_3. Two attempts at an abdominal paracentesis failed to yield any fluid. The patient subsequently again became unresponsive. The peripheral pulses were noted to be present. Gastric suction yielded 2500 ml. of red-brown fluid that gave a ++++ guaiac test. The temperature ranged between 101.4 and 102°F. More Levophed was required

to maintain the blood pressure. Coarse pulmonary rhonchi and basal rales became audible. The urinary output remained small, with subsequent anuria. He died thirty-seven hours after admission.

Differential Diagnosis

Dr. Morton N. Swartz*: I wonder if Dr. Taft would look in the record and tell me whether the "old fried fish" was a red herring.

Dr. Edgar B. Taft: It was a smelt!

Dr. Swartz: This seventy-year-old diabetic man had symptoms referable to both the gastrointestinal tract and the cardiovascular system. To determine whether the primary disease involved both organ systems is part of this problem. The illness began two hours after a meal of old fish. The question about whether the patient had some form of acute food poisoning comes to mind. In general the food poisoning that occurs with salmonella or shigella infection has a latent period of between twelve and thirty-six hours. Acute food poisoning related to staphylococcal enterotoxin usually occurs after a latent period of one to four hours. The cream puff or carbohydrate food is often the source of this enterotoxin, but meat and fish also may be the medium in which the staphylococcus grows and produces its toxin. The fact that the food has been cooked does not rule out poisoning by the staphylococcal enterotoxin since this toxin is relatively insensitive to heat. There was no diarrhea at the onset of this illness or subsequently. Thus, I do not think that I have to dwell on the possibility that the initial episode was any of three usual types of acute food poisoning.

May I see the x-ray films?

Dr. John W. Reeves: In the films of the chest there is a suggestion of slight infiltration of the right base of the lung that may be early evidence of pneumonitis or perhaps early pulmonary edema, although the heart itself is not enlarged and there is no congestion of the pulmonary vascular tree. The striking findings are on the films of the abdomen, in which one can see several loops of dilated small bowel, and as these dilated loops approach the pelvis there appears to be a sudden, perhaps conical, cut-off in the dilated portion of the small bowel. In addition there is a large hernia, which contains separated and dilated loops of small bowel. I do not see any evidence of an opaque foreign body; there is no evidence of free air on the chest film.

Dr. Swartz: Does the stomach appear to be dilated?

Dr. Reeves: The stomach is not excessively dilated. There is a fair amount of air in it. The psoas shadows are clear. The mediastinum is normal.

Dr. Swartz: So-called "indigestion" may be a premonitory sign in acute myocardial infarction. The subsequent development of pulmonary edema and arrhythmias in this patient also suggests this diagnosis. The electrocardiogram gave evidence of ischemia of the anterior wall, but there was no distinct progression of changes to suggest a definite myocardial infarction. The possibility of dissecting aneurysm seems most unlikely in view of the normal pulses and the fact that the aortic shadow was not widened.

The gastrointestinal tract as the source of the underlying disease holds many possibilities, most of which I cannot rule in or out. The patient had a hernia that had been incarcerated for many years and apparently had been asymptomatic. At the time of the onset of illness, during the first twenty-four hours at home and the subsequent twelve to twenty-four hours in the hospital, he did not have any striking abdominal signs. He had no abdominal distention and no abdominal pain until the second and last hospital day. There was no definite evidence of strangulation or bowel obstruction in the hernia. The conical shape of the air pattern in the small bowel, however, raises some questions in this regard.

Another possible underlying lesion is cholecystitis, which may have presented as upper abdominal distress, indigestion and substernal squeezing pain. However, in the absence of striking abdominal tenderness or pain during the first twenty-four hours, I should tend to dismiss the possibility.

Acute pancreatitis, too, is a possibility. The absence of striking localized abdominal signs during the first twenty-four hours of the illness makes me doubtful of this diagnosis. Also, the amylase was normal during the first period of the illness when one would expect it to have been elevated.

Could this man have had acute appendicitis? This disease in elderly persons can be confusing, but the lack of localized signs makes this condition unlikely. Moreover, appendicitis would not explain the large amount of guaiac-positive material in the stomach at the end of the illness.

Could he have had a mesenteric thrombosis or embolus? This seems more likely, although, again, the absence of abdominal pain and lack of evidence of a cataclysmic event during the first twenty-four hours of the illness make me think that this was not the case. The large amount of guaiac-positive material in the stomach tends to focus my attention on the upper gastrointestinal tract.

The last possibility, and one about which I know almost nothing, is acute phlegmonous gastritis. This entity is quite rare and usually is diagnosed only at post-mortem examination. In general it runs a fulminating course and occurs in elderly people, more often in males than in females. By 1945, I think, about 300 cases[1] had been reported in the literature. One of the striking features of the disease is the absence of a clear-cut clinical picture. In general the process is an acute inflammatory one, involving the submucosa of the stomach and extending downward,

*Assistant in medicine, Massachusetts General Hospital.

usually not beyond the duodenum, but occasionally into the duodenum and small intestine. The source of the infection may be hematogenous, or it may be related to direct trauma to the stomach—that is, it may be started by an episode of food poisoning, a gastric ulcer or an ulcerating lesion in a carcinoma from which bacteria may spread in the submucosal tissues.

In view of the repeated episodes of substernal compression and pain, tachycardia and pulmonary edema, I should be hard put to avoid placing some lesion in the cardiovascular tree. I think that the patient probably did have a myocardial infarction during the prolonged period of shock.

I shall stick my neck out and say that I think perhaps the more likely diagnosis is acute inflammatory gastroenteritis, perhaps acute phlegmonous gastritis. I think the patient also had a myocardial infarction. The possibility of an obstructing lesion in the gastrointestinal tract has to be borne in mind.

DR. REEVES: I may not have been entirely fair to Dr. Swartz. I think that this is the picture of small-bowel obstruction; it may not be entirely complete.

Can venous mesenteric thrombosis take this long to develop?

DR. SWARTZ: In view of the course of the illness and the discussion, I think it would be a good diagnosis.

DR. KATHERINE SPRENG: Three features of the case did not fit too well: the man was extremely dehydrated on admission but had no history of any loss of fluid through the urine, vomitus or diarrhea, so that we thought the fluid was being retained within the body; the pulmonary edema responded to the administration of 7 bottles of plasma; before he died we inserted a tube in the stomach and aspirated fresh blood. We believed that he had died from lack of cardiac output as a result of myocardial infarction because he was much better with the loss of fluid. We could not explain the blood in the stomach.

CLINICAL DIAGNOSES

Acute myocardial infarction.
?Gastritis.
?Mesenteric thrombosis.

DR. MORTON N. SWARTZ'S DIAGNOSES

Inflammatory gastroenteritis, ?phlegmonous gastritis.
Myocardial infarction.

ANATOMICAL DIAGNOSES

Esophago-gastroenteritis, pseudomembranous, acute, ?staphylococcal.
Bronchopneumonia, bilateral, severe.

PATHOLOGICAL DISCUSSION

DR. TAFT: At the time this patient came to autopsy he was well developed and well nourished. The prosector could find no evidence of coronary-artery disease of any significance or of a myocardial infarction, either recent or old. There was extensive pneumonia in the left lung and the right lower lobe, which was extremely wet and acute and possibly of the aspiration type. Microscopically, in addition to the acute inflammation, there were small areas of destruction of lung tissue without much reaction.

The primary lesion was an acute esophagogastroduodenitis, with some extension into the jejunum. The lower half of the esophagus, the stomach and the affected small bowel were markedly congested and covered with a yellow fibrinous exudate, which could be peeled away quite easily and left a raw surface underneath (Fig. 1 and 2). In the jejunum the

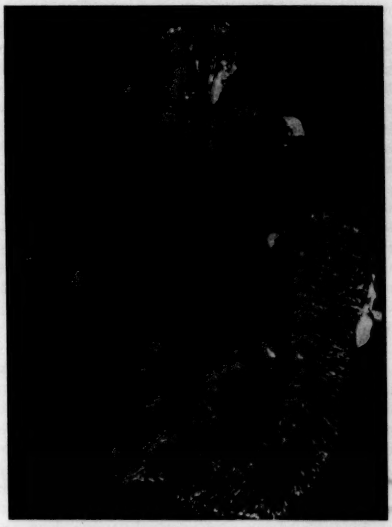

FIGURE 1. *Photograph of the Lower Half of the Esophagus, the Stomach and the Duodenum, Showing Pseudomembranous Gastroenteritis.*

lesions became less confluent. On the outside of the bowel the areas of inflammation could be seen shining through as purplish, discolored areas. Cultures of these membranes were taken, but nothing grew. The patient had been receiving large doses of penicillin for at least twenty-four hours before death so that the lack of bacterial growth is not too surprising. Microscopically, there was severe ulceration, which was compounded to a certain extent by autolytic changes, and there was marked inflammation and edema beneath the mucosa. On staining for organisms, one could find tremendous numbers of gram-

positive cocci in the débris of fibrinous exudate on the surface of the mucosa. The mucosa was markedly altered, although there were some remaining glandular cells at the base. Some of the ducts were filled with fibrin.

Even though we could not culture organisms, it seems that this must have been staphylococcal gastroenteritis of the sort that we have come in the last few years to associate with massive antibiotic therapy, usually after operative procedures and not necessarily associated with previous disease of the gastrointestinal tract.

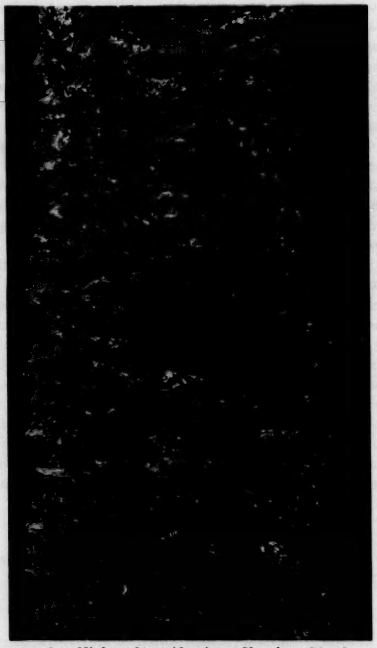

FIGURE 2. *Higher Magnification, Showing Membranous Duodenitis.*

It is always said in discussions of this problem that this disease occurred before the days of antibiotic therapy. This case, of course, is an example of that type of disease. Several times previously I looked in the literature before 1940 for references to such cases and had not found one until today, when I found an article by Blackman[2] from the Johns Hopkins Hospital in 1935. He described this disease in a twelve-year-old Negro girl who ate a large Thanksgiving dinner and in the evening visited friends, with whom she had a "snack" of unknown composition. Five hours later she had severe vomiting that was soon followed by diarrhea and prostration. The family did not believe that she was seriously ill and were upset when they discovered her comatose the next morning. She died one and a half hours after admission to the hospital. Blood culture was positive for *Staphylococcus aureus*. The patient from Johns Hopkins Hospital had a pseudomembranous enteritis involving the jejunum and ileum very similar to that in the patient under discussion. The pictures in the article showed casts of mucous membrane, which are said to be characteristic of this disease.

DR. BENJAMIN CASTLEMAN: Do you think that the fish had anything to do with the illness, Dr. Swartz?

DR. SWARTZ: I was glad to hear it was not a red herring; I think it may well have. I should like to know whether you found any obstructive lesion.

DR. TAFT: There were some adhesions between the loops of sigmoid and the hernial sac, but there was no evidence of obstruction nor was there obstruction elsewhere in the bowel.

DR. REEVES: Did the inflammation extend through to the serosal surface?

DR. TAFT: Yes, there was marked edema throughout the wall of the stomach and the first portion of the duodenum.

DR. REEVES: Could the small bowel be removed from the hernia?

DR. TAFT: There was no small bowel in the hernia; it was all sigmoid.

DR. LAWRENCE KUNZ: What type of specimen was it that gave no growth on culture?

DR. TAFT: Urine and blood had been cultured, but neither revealed growth.

DR. KUNZ: Were any cultures done post mortem?

DR. TAFT: Cultures of the stomach taken post mortem were also reported as showing no growth.

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CASE 42372

PRESENTATION OF CASE

A thirty-six-year-old para 0, gravida 1, housewife was admitted to the hospital because of abdominal pain.

The patient's last normal menstrual period had occurred two months previously. Spotting began six weeks before entry, and there continued to be irregular spotting until five days before admission, when the bleeding increased, although there was not as much as a menstrual flow. For three or four days before entry she had noted increasingly severe pain in the lower abdomen associated with anorexia and with

a marked urge to pass stools frequently. After a pelvic examination on the day of admission there was a sudden sharp pain in the lower abdomen. She then felt very faint and collapsed.

Two and a half years previously a culdoscopy and a dilatation and curettage were performed because of infertility and a dull, aching, intermittent pain in the right lower quadrant that was aggravated during menstruation. The uterus, tubes and right ovary appeared normal; the left ovary contained a follicle cyst measuring 2 cm. in diameter; scattered foci of endometriosis were noted along the lateral portions of the cul-de-sac, especially on the right side; there did not seem to be any ovarian endometriosis; tubal patency was proved by instillation of methylene blue solution through a cervical cannula and the observation of its appearance at the fimbriated end of both tubes. The uterine curettings showed proliferative endometrium. There was a past history of one spontaneous abortion. Six years previously a duodenal ulcer that subsequently healed with dietary treatment was demonstrated in x-ray films. The menarche occurred when the patient was fourteen. The periods were always regular, without excessive flow.

Physical examination showed a slightly pale woman complaining of severe abdominal pain. The abdomen was protuberant and diffusely tender, with spasm and rebound tenderness. Pelvic examination revealed a bloody uterine discharge; the uterus lay anteriorly and was exquisitely tender when moved; there was tenderness in both vaults, greater on the left; a questionable mass was felt in the region of the left adnexa.

The temperature was 100.2°F., the pulse 92, and the respirations 24. The blood pressure was 120 systolic, 82 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 10.9 gm. per 100 ml. and a white-cell count of 14,000, with 88 per cent neutrophils.

An operation was performed one hour after admission.

Differential Diagnosis

Dr. Robert C. Coe*: This, in summary, is a woman in the childbearing age, with six weeks of vaginal spotting and more recently pain in the lower abdomen of sufficient severity to cause her to collapse after a pelvic examination. Culdoscopy, two and a half years previously, had shown endometriosis, a follicle cyst of the left ovary and patent tubes. On admission she was in severe pain and pale and had an elevated pulse rate. The temperature was slightly elevated, and the white-cell count significantly elevated, with a shift to the left. Examination of the abdomen and pelvis gave evidence of an irritating process, most probably in the pelvis, with a questionable mass in the region of the left adnexa.

*Assistant in surgery, Massachusetts General Hospital.

The differential diagnosis must be limited to conditions that are associated with irregular vaginal spotting, severe abdominal pain and a questionable pelvic mass—the three factors that stand out in this case. Acute pelvic inflammatory disease may cause such conditions but should give more historical and laboratory evidence of an infectious process. There were neither chills nor evidence of a febrile course in the four days during which this process built up. One would expect a considerably greater rise in temperature and white-cell count if the findings were on the basis of a pelvic abscess.

A twist of the previously noted cyst of the left ovary would give rise to these symptoms and signs; but, again, one would expect a sicker patient with more evidence of a necrotic process, after a story of three or four days. This diagnosis also seems unlikely in the face of a minimal elevation of temperature and a white-cell count of only 14,000. The line of reasoning would also rule out a degenerative fibroid.

An infected endometrioma of the cul-de-sac might well give rise to such severe pain as this, especially if it leaked, accounting for the pain, the elevated pulse and the pelvic tenderness. However, the history of irregular vaginal spotting does not go with this diagnosis as well as the next one that I shall discuss.

Ectopic pregnancy with rupture fits best into the story and findings presented. It is characteristic in this situation to find a menstrual irregularity, associated with pain, and with a tender pelvic mass—usually either the ectopic gestation itself or clotted blood in the cul-de-sac. We are not given the findings of an examination under ether anesthesia, but I suspect that this confirmed the presence of an adnexal mass on the left. This, combined with a dilatation and curettage, which should have returned decidua, would confirm the diagnosis of an ectopic pregnancy with intraperitoneal bleeding, and a laparotomy was certainly in order.

Clinical Diagnosis

Ectopic pregnancy, with rupture.

Dr. Robert C. Coe's Diagnosis

Ectopic pregnancy, with rupture and intraperitoneal bleeding.

Anatomical Diagnosis

Tubal pregnancy, with rupture and hemorrhage.

Pathological Discussion

Dr. Leonard Atkins: Dr. Green, would you tell us your opinion preoperatively and the findings at operation?

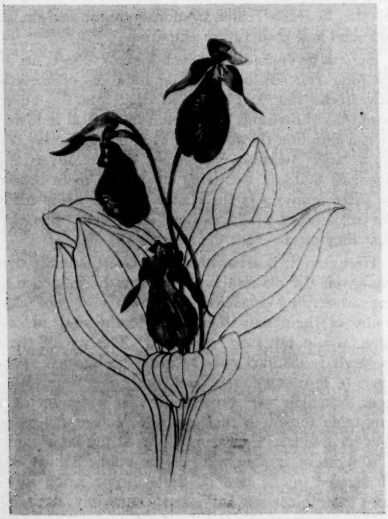
Dr. Thomas H. Green, Jr.: Ectopic pregnancy with rupture was the only diagnosis I seriously considered in this patient, and as Dr. Coe has mentally

done in this exercise, we moved her rapidly from the Emergency Ward to the operating room, a blood transfusion having been started. There was no difficulty in confirming the presence of a mass in the cul-de-sac on examination under anesthesia, and believing that a curettage would contribute nothing further, we proceeded directly with laparotomy.

When the peritoneal cavity was opened, about 500 ml. of blood and clot was evacuated, and a bleeding, ruptured tubal pregnancy on the right exposed. The markedly enlarged, tortuous right tube lay behind the uterus and had become adherent on the left side of the cul-de-sac. Since there had been considerable hemorrhage into the mesosalpinx and right infundibulopelvic ligament, it was necessary to remove the right ovary along with the tube, but I believe we might have considered removing this ovary anyhow. By having only one ovary and this on the side of the one remaining tube, the patient will now both literally and figuratively be putting all of her eggs in one basket. For a woman of thirty-six with a limited number of ovulations left, this might be a decisive factor in the future achievement of a successful pregnancy. As I remember, she had a pedunculated uterine fibroid, which was also removed.

DR. ATKINS: We received the right tube and ovary as well as a uterine leiomyoma, which measured 3 or 4 cm. in diameter. The pregnancy, which was about 3 cm. in diameter, was in the mid-portion of the tube, where there was adherent blood clot at the site of rupture. The ovary was normal.

DR. GREEN: Two other points are worth mentioning in connection with this patient. The first is that the history, symptoms and findings were sufficiently characteristic of an extrauterine pregnancy with rupture to make a preliminary diagnostic culdoscopy unnecessary. It should be remembered, however, that the so-called "classic" cases representing the late stages of this condition are actually in the minority. The clinical picture encountered most frequently with this disease is a much less dramatic one, with vague symptoms and equivocal findings, and in this situation culdoscopy has proved extremely helpful in making a definite diagnosis and in distinguishing other pelvic disorders with similar symptoms, some of which do not require operative intervention. Secondly, the known pelvic endometriosis was barely discernible at this time, presumably having undergone the typical regression with this pregnancy.



MASSACHUSETTS PHYSICIANS ART SOCIETY

45. Pink Lady Slipper

Exhibited at Annual Meeting, Massachusetts Medical Society, 1956

Drawing by
J. D. BARNEY, M.D.
Formerly, chief, Urological Service, Massachusetts General Hospital

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THE PLAY OF THE MARKET PLACE

LAST spring the Federal Trade Commission dismissed its charges of false advertising claims against the company that produces the widely exploited battery additive AD-X2. In so doing the Commission gave greater weight to consumer testimony than to the carefully executed studies of the National Bureau of Standards and of a special committee of the National Academy of Sciences that was asked to make an appraisal of the work of that bureau. The tests made by the Bureau of Standards over a number of years showed that AD-X2 was worthless, like a number of other additives they had examined. The editor of *Science** has properly termed this decision a "test by testimonial."

Such a judgment obviously reflects the tenor of the times. In handing it down an agent of the Government is thus strengthening the hands of the wily and unscrupulous in the commercial and advertising fields who are daily defrauding the public. The decision has the effect of permitting them to sell anything and everything the public is willing to buy and at the price it can be induced to pay.

Perhaps it is of little consequence that millions of people, as a result of this decision, will pay a few extra dollars for a pinch of salt added to their batteries, even if it has no value whatever. But the philosophy and the attitude behind the decision will have more far-reaching and devastating effects on the morale of the Federal Trade Commission and of similar agencies and their future activities.

Such a downgrading of moral issues reflects an increasing concern over the degradation of medical advertising that has extended even into the otherwise ethical divisions of the pharmaceutical industry. It is a situation the responsibility for which may rest in a large measure on certain of the advertising agencies that are becoming constantly more brazen or more insidious in the claims that are being made for all kinds of products, both useful and otherwise, that they promote for their clients.

Here, too, it is often the "test by testimonial" that has given the manufacturers, under the influence of the advertising agencies, the courage to do what many of them may themselves loathe and, at one time, would not have condoned. The use of these methods is justified only because the business managers of so many commercial enterprises seem to believe that their sole responsibility lies in producing a profitable return to their stockholders, and because they have to beat their competitors at the same game. The sense of responsibility to the public, which was discharged in the past by the self-monitoring processes of ethical industry, has noticeably declined, owing perhaps to the failure of a few members of an industry to abide by the rules that once guided it, and

*Editorial. Test by testimonial. *Science* **123**:1059, 1956.

also because it is in keeping with the manners and mores of the times.

The medical profession apparently condones these practices, and even its own monitoring agencies seem to have been letting down their guard. This has been done, again, in the favoring climate of good business, unparalleled prosperity and equivocal legal decisions. It may be hoped that before too long there will again be a desire for reform similar to that which gave origin to the Food and Drug Administration, such laws as the Food, Drugs and Cosmetics Act, and the establishment of the Federal Trade Commission. This may and should come soon in the pharmaceutical field because here the lives and health of the people are at stake and cannot be jeopardized for the sake of any amount of profit.

Even where decency and reasonable safety are not violated the trends of the times are obvious. The advertising programs of the most conservative pharmaceutical manufacturers have fallen under the spell of the youngest of the estates — the guild of the advertisers — the trade that, operating under its own ethical standards, aspires to become a profession. One need only compare the glamour of the advertising pages of any medical journal that reaches the practitioner today with the drab content of those same pages five years ago to appreciate the present dilemma of the editor, to say nothing of that of the manufacturer, with all the amazing products of modern pharmacology at his hand and the need in some way of keeping pace with his competitors.

And yet with the majority of the manufacturers, especially the old and established houses whose names are found in the majority of the journals, the desire remains to hold their advertising propensities in check, to serve their public and the medical profession well and to make capital of honesty and integrity. In conjunction with such a straightening of the line a conscientious and public-spirited attitude on the part of the business community would be the strongest bulwark against encroachments by the Government on private enterprise.

POLIOMYELITIS FOUNDATION FELLOWSHIPS

THE National Foundation for Infantile Paralysis announced in August a wide range of generously financed fellowships to be awarded on application for postdoctoral study. Although applications for these fellowships may be submitted at any time, according to the Division of Professional Education of the Foundation, three deadlines relate to scheduled meetings of the reviewing committees: September 1, 1956, a date too imminent at the time of the release to have been effectively announced in these pages; December 1, 1956, and March 1, 1957.

Fellowships are offered, specifically, for postdoctoral training in research or academic medicine or both, to applicants with an M.D. or Ph.D. or suitable equivalent degree; for postdoctoral study in the clinical fields of rehabilitation, psychiatry, orthopedics, the management of poliomyelitis, and preventive medicine; for medical students who wish to make short-term studies in research, public health, preventive medicine or rehabilitation, and for students in the medical associate fields. This classification includes physical therapists, to prepare for teaching; health educators from state health and education departments to study in an approved school of public health, and social scientists to apply their professional skills to the emotional problems of patients with physical disabilities. Scholarships are also awarded for the basic professional education of medical social workers and physical therapists.

Financial support of these fellowships is variable. For a full academic program, according to the statement, tuition and fees are paid, and for other programs a sum not to exceed $1250 per year. More specifically, for postdoctoral training in research or academic medicine or both and for psychiatrists interested in the emotional problems of patients with physical disabilities, financial benefits range from $3600 to $6000 a year. For orthopedic surgeons and physicians interested in the teaching of preventive medicine the same benefits (in addition to the compensation to the institution) vary from $4500 to $6000 annually. For physicians interested in rehabilitation or wishing specialty training in the subject and for those wishing to acquire a knowledge of the total care of poliomyelitis patients the financial benefits are $300 or $350 per month, depending on marital status, with $25 additional for each dependent child.

The total sum that the Foundation has authorized since 1938 for scholarships and for aid to educational institutions, professional organizations and the like is $23,500,000 — a large sum indeed to have been collected from the public almost literally dime by dime. It must be remembered also, in an appraisal of the vast task that the Foundation has undertaken, that this sum is in a way a surplus beyond that which has been expended on the purposes for which the dimes were presumably given — the direct care of poliomyelitis patients and, more lately, the prevention of this evil disease. Education and research in all fields of medicine must be pursued with vigor, however, and certainly no generous contributor to the Foundation would see any impropriety in having his donation applied to any branch of medical study that might in any way have bearing on the care of the poliomyelitis patient.

Moreover, as was announced over a year ago by the director of the Foundation, now that poliomyelitis is virtually conquered, the organization must find other fields into which to direct its energies and in which to expend its resources.

PEMMICAN, PERHAPS

A REPORT of the British Public Health Laboratory Service on food poisoning, discussed in a leading article in the *Lancet*[1] last winter, lists 39 per cent of all such enteric mishaps as of cause unknown. Such a percentage of epidemiologic failures is too high, according to the *Lancet*, and few would disagree.

Salmonellae were found to be responsible for more than half the "food-poisoning" incidents of 1954 whose cause was determined, with staphylococci and clostridia making up only 2 per cent and 1 per cent respectively of the total. Since many isolated outbreaks of salmonella infection are not traced to their source, their designation as the result of food poisoning may sometimes be in error.

That which milkmongers, were there such a word to cover this category of tradesmen, might call reconstituted meat is a notable offender in the etiology of enteric diseases of infectious origin. Made-up and even commercially tinned meats have been found responsible for 170 out of 250 outbreaks of proved cause, reheated or, in the vernacular, hotted-up meats being especially morbific.

The Food and Drugs Amendment Act of 1954 is "a pointed example of the difficulty of regulating the trivialities of daily life by the written word. It creates new offences but offers little hope of greater rewards here or hereafter. . . . Legislation which runs too far ahead of public opinion seldom has its designed effect."

A passage in the Act, which became effective on January 1, 1956, relates to the offense, now become penal, of smoking while handling any open food or while working in any food room where food lies unprotected.[2] The smoke of the tobacco is considered in no wise curative to the product, and the rule obtains regardless of whether the food had been previously smoked by scientific or traditional methods. The editor of the *Lancet* suggests, with considerable justice, that the medical officer of health, before beginning still another campaign to the purpose of banishing salmonella and other offending organisms, "might give some thought to adding to our knowledge of the essential causes of food-poisoning."

The latest installment in the recital was published on June 2, when the *Lancet* reported the case of a grocer, not necessarily green, of Acton, London, who, having previously been warned of his liability, was fined £6 and 2 guineas costs for smoking a pipe while at his bacon slicer, with uncovered bacon and cheese nearby.[3]

To the grisly risks of smoking with which the public has been impressed in the last few years, that of having a bacon slicer nearby can be added, at least in Merry England.

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It will, we think, be universally conceded, that the main objects of a medical journal are to afford a medium of expression to those whose communications are of real value, and which, consequently, advance medical science and the public weal; next, to be the archives for facts worthy to be treasured up for future reference; to prove the vehicle of question and answer upon the important topics of physiological, pathological, therapeutical and hygienic discoveries, to be the independent arbiter of professional literature; and, finally, to endeavor to unite, by a pleasant influence, all "good men and true" in the bonds of professional friendship.

Boston M. & S. J. *September 18, 1856*

MASSACHUSETTS MEDICAL SOCIETY

TOXIC HAZARDS*

FATAL POISONING FROM TOPICAL USE OF BORIC ACID POWDER†

Fatal boric acid poisoning has been reported many times, not only from accidental ingestion and infusion of boric acid solutions[1] but also from the application of pure boric acid powder to denuded or inflamed skin lesions of infants.[2,3] A fatal case recently seen at the Children's Medical Center, Boston, re-emphasizes the hazards of this therapy.

A 3½-month-old male infant was admitted to the hospital for the treatment of vomiting, diarrhea, lethargy and dehydration. Five days previously the mother had consulted the family physician about a diaper rash, and had been advised to apply pure boric acid powder to the involved skin, which she did every 2 hours up to the time of admission.

On admission a raw, erythematous, desquamating rash was present over the diaper area, on the face and on the palms and soles. The conjunctivas were red and crusted. A rotary nystagmus and internal strabismus were noted. Reflexes were symmetrically hyperactive. No meningeal signs were present, and the fontanel was flat.

Routine urinalysis was negative, and a hemogram was normal. The nonprotein nitrogen was 65 mg. per 100 ml. Other blood chemical findings were within normal limits. Lumbar puncture was normal. X-ray examination of the skull showed increased intracranial pressure. A tumeric acid paper test on the urine and cerebrospinal fluid was positive.

The infant received intravenous infusions of fluids and antibiotics. On the 2d hospital day he began to vomit coffee-grounds material, and became unconscious. Convulsions started which could not be controlled with pheno-

*This is one of a series of articles published co-operatively by the Committee on Industrial Health and the Panel on Child Health of the Committee on Public Health of the Massachusetts Medical Society. The panel provides liaison with the Massachusetts Chapter of the American Academy of Pediatrics whose Boston and Worcester Poison Information centers are activities of its Committee on Accident Prevention.

†From the Boston Poison Information Center.

barbital. On the third hospital day peripheral vascular collapse became apparent, and the child died despite supportive measures.

At autopsy cerebral edema, fatty infiltration of the liver, and massive unilateral adrenal hemorrhage were found. Focal hyperemia (but no ulcerations) was present in the duodenum.

Quantitative boron determinations (Table 1) later substantiated the diagnosis of boric acid poisoning.

TABLE 1. *Determination of Boron and Boric Acid.**

ORGAN	CONCENTRATION	
	BORON	BORIC ACID
	parts/million	*parts/million*
Brain	17.9	94.5
Liver	46.0	242.0
Ante-mortem serum	133.0	720.0
Post-mortem serum	87.0	460.0
Normal value	< 1.0	5.0 or less

*Kindly performed by Johnson & Johnson Co., New Brunswick, New Jersey.

Bloody vomitus and diarrhea, encephalitic signs and a characteristic erythematous desquamation, especially of the palms and soles, are the cardinal manifestations of boric acid poisoning. The mortality in patients with these findings is about 70 per cent. The toxic amount for infants is not known, but appears to be small since as little as 1 gm. has caused death after ingestion.

A presumptive diagnosis of boric acid poisoning can be made from the characteristic history and clinical picture. The tumeric acid paper test, although useful, is not too reliable, since a number of false-positive reactions occur.[4] Quantitative colorimetric methods are now available to confirm a suspected case.[5]

Symptomatic treatment, including fluid replacement and sedation, is quite ineffective, as shown by this case and the experience of others. Exchange transfusion, when performed before irreversible tissue damage has occurred, is at present the best available therapy.[6]

Prevention, of course, is the best treatment. With the multitude of effective agents available for the prevention and treatment of diaper rash, the use of pure boric acid powder for this condition is unwarranted. The use of small amounts of boric acid (3 to 5 per cent) as a buffering agent in talcum powders has, however, been shown to be without danger.[7]

Boric acid is probably harmless when applied to the intact skin, but, as shown by the case summarized above, has considerable danger when applied to broken skin and should never be prescribed in such cases. Physicians should also warn parents not to use this popular home remedy for skin lesions of infants.

FRED S. ROSEN, M.D.
ROBERT J. HAGGERTY, M.D.

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MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

STAPHYLOCOCCAL INFECTIONS OF THE NEWBORN

In the *Journal of the American Public Health Association* for July, 1956 (p. 854), there appeared a note from Dr. Thomas E. Shaffer, of Ohio State University, stating that a single strain of *Staphylococcus pyogenes* has been responsible for all lesions in a recent outbreak of staphylococcal infections among newborn infants in the nurseries of the University Hospital. Most of the strains studied show identical patterns of antibiotic sensitivity. Dr. Shaffer invited the readers to send to him cultures obtained from pustular lesions of infants or purulent lesions from nursing mothers during nursery outbreaks of epidemic proportions, for bacteriologic study.

At the time the *Journal* appeared, the Diagnostic Laboratory of the Massachusetts Department of Public Health had just been studying a staphylococcus from an infant who had died during a nursery outbreak. The Laboratory sent a subculture to Dr. Shaffer, who reported it to be of the same type as strains isolated from eighteen different widely separated epidemics of staphylococcal infections in infants and nursing mothers.

These results are of considerable interest, and warrant further investigative studies. It is suggested, therefore, that if a nursery infection of *Staph. pyogenes* should break out in any hospital, a culture may be sent to the Diagnostic Laboratory for submission to Dr. Shaffer. If it is preferable to send the culture directly to Dr. Shaffer, one should also be sent to the Diagnostic Laboratory. The address to which the specimens should be sent is:

Dr. Robert MacCready
Diagnostic Laboratory
281 South Street
Jamaica Plain 30, Massachusetts.

CORRESPONDENCE

REGARDING HYPERGLOBULINEMIC PURPURA

To the Editor: I read with interest the very fascinating article, "Idiopathic Benign Hyperglobulinemic Purpura," by Seiden and Wurzel in the July 26 issue of the *Journal*, purporting to be the second reported case in the United States. In my capacity as officer in charge of the Contagious Disease Section of the 3275th USAF Hospital last year, I was confronted with bizarre rashes in many patients referred to our section because of suspected exanthematous disease.

Hyperglobulinemic purpura, essential and symptomatic cryoglobulinemia and macroglobulinemia were considered in the differential diagnosis in 4 cases, but limitations in time and facilities prevented precise classification of these patients. A thorough review of the available literature at that time uncovered an additional report of 13 cases of hyperglobulinemic purpura (Waldenström), embellished by electrophoretic studies, by Wilson, Bolinger, and Slinker of Kansas City, Kansas, on page 953 of the *Journal of Laboratory and Clinical Medicine* for December, 1954.

Giving credit where justly deserved, this would make the case reported by Seiden and Wurzel the fifteenth in the American literature.

HAROLD P. LAZAR, CAPTAIN, USAF (MC)
Parks Air Force Base, California

COLOR OF PENICILLIN

To the Editor: Your issue of July 12, 1956, contains an article entitled "Current Concepts in Therapy." This addition to your wonderful journal will be of inestimable value. However, I nearly fell out of my armchair when I read on page 88 that "Penicillin is a stable yellow powder . . ." While it is true that in the early 1940's a book entitled *Yellow Magic* was published, pure white crystalline sodium and potassium penicillin G was first prepared in 1946. For the past ten years only white penicillin has been available on the market.

At the United States Food and Drug Administration we have for display purposes a few samples of the impure brownish penicillin from the earliest production in the country. As penicillin became purified the brownish color gave way to yellow and eventually all coloring matter was removed as penicillin was crystallized.

LAWRENCE E. PUTNAM, M.D.
Associate Medical Director
Antibiotics Branch
Bureau of Medicine
Washington, District of Columbia

Dr. Putnam's stricture was referred to Editorial Board member Friend, the *Journal's* expert on pharmacologic problems, who offers the following reply:

To the Editor: The comments made by Dr. Putnam concerning the color of highly purified penicillin powder are correct. The experience of most physicians who handle penicillin, however, is that there is usually a slight tinge of yellow to the preparations commonly handled in the office. This yellowish tinge is due to impurities.

It should be noted that the 15th edition of the *Pharmacopoeia of the United States* describes potassium penicillin G as a white to slightly yellow crystalline powder. Impurities can vary from batch to batch of penicillin since the *Pharmacopoeia of the United States* requirements are that potassium penicillin G for example, contain not less than 90 per cent of total penicillins, calculated as potassium penicillin G. Most manufacturers prepare products with a much higher degree of purity than required by the *U. S. P.* There is, however, the possibility for impurities still to be present in our much more refined penicillin preparations. This may vary, depending upon the batch and the manufacturer. Some potassium penicillin G preparations contain as much as 99 per cent pure penicillin — others contain less, but all meet the required amount of 90 per cent or better. Most penicillins prepared by competent manufacturers contain well over 90 per cent total penicillin and are pure white powders.

Of course if penicillin stands exposed to any amount of light or air or is put up in various oils there is a definite tendency for the yellowish color to reappear.

DALE G. FRIEND, M.D.
Boston

REGARDING ESTROGEN THERAPY

To the Editor: In a Medical Progress article entitled "Some Abuses of Drugs in Therapy" *(New Eng. J. Med.* **254:** 1223-1231, 1956) Friend and McLemore express a not uncommon view that "Perhaps of all the hormones, the estrogens are most widely used and abused." They describe a forty-year-old woman oöphorectomized at the age of eighteen years who developed vasomotor symptoms whenever her prolonged estrogen therapy was withdrawn. They conclude that this is a case of "physical dependence created by the use of hormones" and recommend withdrawal of the drug and avoidance of future use in such patients.

The extensive experience of Dr. Fuller Albright and his associates in the Ovarian Dysfunction Clinic of the Massachusetts General Hospital has led us to the contrary view. Prolonged estrogen therapy of a girl bilaterally oöphorectomized at eighteen years of age is better termed *replacement* therapy, since estrogen secretion normally continues until the age of forty-five years and often well beyond. Nervous and vasomotor symptoms on withdrawal of estrogens are associated with and probably due to compensatory increase in gonadotropin secretion. Addiction is not the proper term to apply to such symptoms any more than it is correct to term the diabetic person "addicted" to insulin or the patient with Addisonian disease to cortisone.

Extended follow-up study of oöphorectomized young women has revealed the extensive damage to the skin, bones and nervous system that results from prolonged lack of estrogens. It is the experience of the Ovarian Dysfunction Clinic that estrogens are effective treatment and prevention for postmenopausal osteoporosis as well as for the incapacitating nervous symptoms that may follow castration. Prolonged estrogen therapy does not appear to have been associated with an increased incidence of genital and breast cancer; indeed, it is our impression that such cancer is less common in the group of patients to whom we administer prolonged estrogen therapy.

PHILIP H. HENNEMAN, M.D.
ANNE P. FORBES, M.D.
Boston

Note: The letter printed above was shown to Drs. Friend and McLemore who offer the following reply. — ED.

To the Editor: The letter by Dr. Philip Henneman and Dr. Anne Forbes is interesting and we agree that in certain patients it is necessary to administer estrogen for varying periods. Certainly, there is nothing in our article that precludes the proper use of estrogens or any other medicinal agent when there is reasonable clinical and laboratory supervision. It is not our intention to have anyone discontinue the use of estrogens when they are indicated, but initiation and routine administration of estrogens over long periods without adequate observation are certainly not good medical practice and not in the best interest of the patient. It is not at all clear as yet that the vasomotor phenomena are due to compensatory gonadotropin activity. Such phenomena are not uncommonly observed in anxiety states, after certain drugs and following the withdrawal of many addiction-producing drugs.

Regarding the writers' comments concerning addiction, there is nothing in our paper that implies that estrogens are addicting drugs. What we said was that there actually are cases of dependence created in certain patients by the use of hormones; for example, a patient made a thyroid cripple by long administration of thyroid substance develops such dependence. What we attempted to point out is that these agents must be adjusted to the patient's needs and that only the amount demonstrated as necessary by repeated clinical and laboratory evaluation should be given. When they are

no longer needed they should be reduced and withdrawn as promptly as possible. Regardless of whether estrogens do or do not increase the incidence of carcinoma of the breast or genital tract, no one would wish to give them in the presence of these tumors. Unless adequate clinical and laboratory follow-up is carried out, that is just what can and does happen. Finally, the prolonged and unwarranted administration of hormones is a source of needless expense to the patient.

DALE G. FRIEND, M.D.
GEORGE A. MCLEMORE, JR., M.D.
Boston

REGARDING "CURRENT CONCEPTS IN THERAPY"

To the Editor: I read the *Journal's* section entitled "Current Concepts in Therapy" and your editorial with considerable interest. I think this program is a very commendable one. I should like to make a suggestion–namely, that whenever possible, the organic structural formula be included. This offers a better basic understanding of the relation of various preparations we are being overwhelmed with, as well as a means of ready reference.

JACK D. COHEN, M.D.
Boston

PERIODIC HEALTH EXAMINATIONS

To the Editor: The following letter from the acting secretary of the Council on Industrial Health of the American Medical Association expresses an important need for a certain type of information.

As chairman of the Committee on Industrial Health of the Massachusetts Medical Society I shall be happy to receive and pass on to Dr. Bridges the information that he seeks relative to this commonwealth.

Dr. George F. Wilkins, Chairman
Committee on Industrial Health
Massachusetts Medical Society
245 State Street
Boston 9, Massachusetts

Dear Dr. Wilkins:

The increasing interest in Periodic Health Examinations for Executives has resulted in our receiving numerous requests from medical directors and top management personnel for information on the subject. Most often, we are asked to furnish a list of clinics specializing in this type of examination.

We would like to prepare a comprehensive, nation-wide list of physicians, clinics and hospitals having a particular interest in this field. To accomplish this, we are asking the Committees on Industrial Health in the various States to assist us by listing known facilities in their states on the attached form and returning it to us. The list will not be published, but will be duplicated and used by us solely to answer inquiries. However, we have agreed to share the information we develop with the Metropolitan Life Insurance Company in return for similar data they are assembling.

Your cooperation will be greatly appreciated.

Cordially,

CLARK D. BRIDGES
Acting Secretary
Council on Industrial Health
American Medical Association

G. F. WILKINS, M.D.
New England Telephone and Telegraph Company
245 State Street
Boston

PET PEEVES

To the Editor: I remember a cartoon strip many years ago, entitled "Pet Peeves." It apparently served a useful purpose in permitting the reader to enjoy the realization that others had similar annoyances.

One source of annoyance or peeve that has been increasing over the past few years and has been undoubtedly encountered by other physicians is the members of a patient's family who ask usually about an elderly parent, "Nothing can be done — there is no treatment, is there, Doctor?" Often, the question is deliberately asked in front of the patient so that he can hear it and understand its purpose. I have found that too often, various members of the family have already decided, for economic, personal or selfish reasons, to shirk their responsibilities and need a soothing salve for their consciences. To accomplish this, they try to badger or trap the physician into their camp. At the same time, they try to impress upon the patient the hopelessness of his case so that their negligence is not evil.

My solution is to reprimand or lecture the shirker. It is often successful.

ROY J. POPKIN, M.D.
Los Angeles

BOOK REVIEWS

Kinesiology of the Human Body: Under normal and pathological conditions. By Arthur Steindler, M.D. (Hon.) F.R.C.S., Eng. F.A.C.S., F.I.C.S. 4°, cloth, 708 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1955. $19.75.

This is both an excellent and comprehensive study of the mechanics of joint function in both health and disease. The author presents an exhaustive review, devoting a chapter to the pathomechanics of individual joint dysfunction in disease, presenting not only a clearly worded review of the alterations the joint undergoes in pathologic conditions but also, by the use of very clearly drawn diagrams, a clear-cut analysis of different states. This is not a book that deals with the treatment of diseases but one that describes in detail what takes place in the various joints under conditions of altered mechanics. This textbook can be recommended to the clinical orthopedic surgeon interested in detailed analysis of joint function and general body mechanics; also, it is to be recommended as an excellent general source book, illustrating many of the basic fundamental principles of joint function in both normal and abnormal states. Emphasis is placed upon the clinical significance and practical advocation of these fundamental principles.

HARRISON O'CONNOR, M.D.

Segmental Anatomy of the Lungs. By Edward A. Boyden, Ph.D.(Med.Sc.). 4°, cloth, 276 pp., 125 illustrations, 37 tables and 12 colored plates. New York: The Blakiston Division, McGraw-Hill Book Company, Incorporated, 1955. $15.00.

This volume is written by one of the most distinguished anatomists in this country. The anatomic approach to the problem is in the highest tradition of scholarship. The text begins with an instructive historical review, followed by a discussion of the criteria that must be established to judge variations. The Jackson–Huber terminology is retained in the interpretation of these criteria. The various lobes of the lung are dealt with under the headings of surfaces, bronchial distributions and arterial and venous patterns. It is emphasized, however, that to gain an integrated concept of the lungs, it is necessary to deal with both these aspects. The chapter on the development of the lungs and the formation of gross congenital anomalies will prove very fruitful to all students in this field. The author makes clear that variations occurring in one direction are compensated for in another; consequently, an interpretation of developmental processes can best be appreciated from the holistic point of view. The text ends with a discussion of the lungs as a whole illustrated by exquisite color plates and concise descriptive legends.

A splendid feature of this book is the bibliography. It appears to the reviewer that this authoritative work will take its place with the classics of American anatomic research; it offers the medical profession a well balanced account of the lungs — one that every physician will unquestionably wish to have on the shelves of his library.

BENJAMIN SPECTOR, M.D.

Psychocutaneous Medicine. By Maximilian E. Obermayer, M.D. 8°, cloth, 487 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1955. $9.75. (Publication No. 239, *American Lecture Series.*)

This volume, as its title implies, considers the aspects of two disciplines — psychiatry and dermatology — that are of interest to both.

It embraces a wide variety of topics. These extend from trichotillomania and delusions of parasitosis at one extreme to acne vulgaris and lichen planus at the other. The various skin diseases are arranged according to a broad spectrum. Some conditions are almost purely psychiatric (syphilophobia). Others, such as seborrheic dermatitis and baldness, are of psychologic interest only because of their effects or their complications.

Some of the most interesting sections concern neurodermatitis or atopic dermatitis, urticaria, acne rosacea and lupus erythematosus. Reports on these conditions that have appeared in the literature are concisely summarized. Personality, precipitating causes and the pathological physiology are all discussed. The writer adds his own observations to the many authorities cited.

There are sections on psychodynamics, psychologic methods, physiology, Selye's alarm reaction and methods of treatment. Over thirty cutaneous diseases are covered, with some excellent photographic illustrations. Although not sufficiently organized to be used as a textbook, the work is stimulating and contains many useful suggestions.

HERBERT BARRY, JR., M.D.

Integrated Gynecology: Principles and practice. In three volumes. By I. C. Rubin, M.D.; and Josef Novak, M.D. 8°, cloth, 1869 pp., with 511 illustrations. New York: The Blakiston Division, McGraw-Hill Book Company, Incorporated, 1956. $60.00.

Drs. Rubin and Novak, two of the world's outstanding gynecologists, have combined their lifelong experiences in the clinical and research aspects of gynecology to produce this outstanding and invaluable contribution.

In this three-volume work virtually every aspect of gynecology is thoroughly covered, from anatomy and physiology to therapy and operative gynecology. Within the confines of these and other chapters both the commonplace and the unusual are extensively covered.

Half the third volume is devoted to the relation of gynecology to the various other body symptoms. It is this section that gives the work its special flavor and represents a unique contribution on the part of the authors. It is in keeping with the growing concept that gynecology is not merely the study of the female pelvic organs but also an over-all science concerned with women in health and disease. This is the argument against those who say that the outlook of the specialist has become too narrow. On the contrary, the modern specialist must be familiar not only with the system of his specialty but also with all systems. There are excellent chapters on the reciprocal relation between the female reproductive tract and the urogenital system, the endocrine glands and the psyche, as well as others.

Another excellent feature of the work is the extensive bibliography, which is well outlined after each section. Few textbooks can match this for thoroughness. However, there is a tendency on the part of the authors to rely on older publications. The illustrations, too, are often from older textbooks. This is particularly noticeable in the section on operative gynecology. The general surgeon may be confused by the multiplicity of technics described in this section, as well as in the section on therapy.

The sections on endocrinology and tumors are especially thorough and interesting.

To the general practitioner or general surgeon the volumes cover the field with the thoroughness of a reference book. Perhaps there is too much emphasis on historical background for the occasional worker in the field. But this feature, together with the extensive references, will be of supreme interest and value to the specialist.

MELVIN L. TAYMOR, M.D.

Lehrbuch und Atlas der Anatomie des Menschen. By Prof. Dr. Fr. Kopsch. Vol. 1. 19th edition. 4°, cloth, 736 pp., with 731 illustrations. Stuttgart: Georg Thieme, 1955. DM. 64.50. $15.35. (Distributed in the United States by Intercontinental Medical Book Corporation, New York.)

This is the nineteenth, thoroughly revised, improved edition of a standard textbook and atlas of human anatomy. The author declares his conviction that without sufficient knowledge of form one cannot understand function. This is a healthy point of view, and many students and clinicians will turn to this book for this very reason.

The stained microscopical figures are beautifully printed, and the gross pictures are superbly represented. The first volume deals with the skeletal, muscular and vascular systems; the second treats of the nervous system and the sense organs. These two volumes should be available for reference in all medical libraries.

BENJAMIN SPECTOR, M.D.

Grundriss und Atlas der gynäkologischen Cytodiagnostik. By Dr. H. Smolka, and Dr. H. J. Soost. With a foreword by Prof. Dr. E. Philipp. 4°, cloth, 166 pp., with 186 illustrations and 6 figures. Stuttgart: Georg Thieme, 1956. DM 120.- $28.55. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

This book is another in the growing list of competent textbooks on cytologic diagnosis. The authorship is unique since one of the authors is a doctor of medical sciences associated with a manufacturer in Mannheim who processed and underwrote the cost of numerous excellent color plates. The volume is outstanding in its size and the quality of its paper, printing and illustrations.

The arrangement of contents is relatively standard. There are excellent chapters on methods and on the morphology of normal cells. One unusual and particularly useful chapter is devoted to the subject of the normal vaginal cytology as it varies throughout the lifetime of the human female. The chapters on cytologic changes secondary to hormonal variation and vaginal infection and the chapter discussing the value of cytology in hormone diagnostics would all three be considered controversial by those who study in this field. However, the authors' case is presented clearly and intelligently. It is important only for the reader to remember that other interpretations are possible.

Chapters on pregnancy and its complications, chronic inflammatory and other local lesions and neoplastic disease present almost entirely the facts as observed through the microscope, and these chapters compare favorably with similar ones in other atlases. A brief review of the changes seen with radiation therapy for carcinoma limits itself entirely to a description of these changes, with only a passing mention of the prognostic value of such a study.

Finally, there are brief chapters on methods of studying the cytology in ascitic fluids, the use of the phase-contrast microscope in cytologic study, and a suggested method of recording and filing cytologic observations.

In summary, this is a very expensive but very well printed and organized atlas that completely covers the subject of its title. It will undoubtedly be used for reference by those who are interested in the subject and familiar with written German. Its most important contribution to the literature on the subject to date is the chapter on cytologic variations at different ages.

HOWARD ULFELDER, M.D.

Allergy in Childhood. By Jerome Glaser, M.D. 8°, cloth, 529 pp., with 42 illustrations and 39 tables. Springfield, Illinois: Charles C Thomas, 1956. $12.50. (Publication No. 272, *American Lecture Series.*)

Dr. Glaser has written a very readable monograph. The chapters are brief and cover each topic concisely. A bibliography at the end of each chapter and, in some places, after a particular section within a chapter makes for quick and easy reference. The printing is excellent.

Since this volume is not presented as a reference or definitive textbook the inclusion of unconfirmed material appears unnecessary, and undesirable. This is especially so when, for example, the author refers to procedures published six to sixteen years before and, at the time of his writing (1955-1956), "awaits further clinical evaluation in children," and again "the general use of this procedure [aerosols of certain drugs] awaits confirmation of other investigators." It is unfortunate in the light of recent work to the contrary that the following statement appears: "Phenylpyruvic Oligophrenia is not amenable to treatment."

Objection can be raised to the propriety of recommending a drug so controversial as Demerol in status asthmaticus. Since this book is slanted toward the practitioner and not the expert it would have been wiser to omit such a recommendation. In defense of Dr. Glaser, he does qualify his use of this drug. It is to be regretted that the surface-area method of dosage was not used in this volume. The great variation in the size of infants and children makes such a method desirable. The procedure recommended for testing sensitivity to local anesthetics seems cumbersome and not likely to be used by many.

There is considerable difference of opinion in various clinics about the indications for specific treatment in pollenosis and the aspects of prophylaxis of allergic diseases as championed by Dr. Glaser, but as he states in the introduction "it [pediatric allergy] is a young specialty," and such differences are to be expected. The book as a whole fulfills the promise of the statement on the jacket, "Real help for the Pediatrician . . . who has a problem in this field."

LEO B. BURGIN, M.D.

Correlative Neurosurgery. By Edgar A. Kahn, M.D.; Robert C. Bassett, M.D.; Richard C. Schneider, M.D.; and Elizabeth Caroline Crosby, Ph.D., M.D. With a foreword by Kenneth G. McKenzie, M.B., Toronto, F.R.C.S. (C). 4°, cloth, 413 pp., with 235 illustrations and 8 tables. Springfield, Illinois: Charles C Thomas, 1955. $19.50.

This volume summarizes the neurosurgical policies and practice of Dr. Edgar A. Kahn's service at the hospital of the University of Michigan; 15 authors wrote it. A special feature is the series of sections by Dr. Elizabeth C. Crosby correlating neuroanatomic and neurophysiologic facts with those in the pertinent clinical realm and interspersed appropriately in the text. This arrangement amply justifies the title of the volume and contributes hugely to its value. The general level of merit of the chapters by the various contributors is such that I have been led to read the whole volume with care instead of skimming through it, and have been greatly helped by it in preparing a section on neurosurgery for a general textbook on surgery. Dr. White and I recommend this book to our residents in training as perhaps the best to give sound practical advice over the whole field of neurosurgery along with a lucid discussion of the principles on which the advice is based. The unwieldy size of the book, 8¾ by 11¼ inches, was dictated by a desire to have large, effective illustrations. The quality of these probably justifies the minor inconvenience.

The practicing neurosurgeon with the conventional type of training will probably be grateful in particular for a chapter by the plastic surgeon, Converse, on the closure of difficult scalp defects, since he may have seen few of these himself. The contributions by the neurosurgeons in the group are uniformly first class. They have omitted consideration of benign intracranial hypertension (pseudotumor cerebri or meningeal hydrops), of arachnoiditis causing hydrocephalus or spinal symptoms, and of the surgical treatment of the epilepsies in an otherwise comprehensive survey. Detailed discussions of trauma, both craniocerebral and spinal, are well handled and properly lengthy because of the importance of the subject to all neurosurgeons. Concise chapters are provided on the aphasias by R. N. DeJong and on endocrine and metabolic facts in relation to neurosurgery by J. M. Bauer. These give a useful summary of the really important facts culled from the labyrinthine mass of information in both fields. The chapters on localization of tumors by the electroencephalogram and by radioactive isotopes overemphasize the technics used by the authors; their value remains to be proved by others. The reader will need to consult other work for an adequate bird's-eye view of these two topics.

But the volume as a whole would certainly be a source of pride to the late Professor Max Peet, Michigan's great neurosurgical pioneer, who trained all the neurosurgical authors of the book.

WILLIAM H. SWEET, M.D.

Pädiatrischer Röntgenatlas: Eine Sammlung typischer Bilder. By Dr. M. A. Lassrich; Prof. Dr. R. Prévôt; and Prof. Dr. K. H. Schäfer, Hamburg. 4°, cloth, 333 pp., with 700 illustrations. Stuttgart: Georg Thieme, 1955. DM 115.- $27.40. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

This book, by the authors' own statement, is intended to fill the gap left by twenty years since the last publication of a German pediatric radiologic textbook. It is not intended to cover the same material so well presented in English by John Caffey, *Pediatric X-Ray Diagnosis.*

The book is truly an atlas, a collection of 700 x-ray films well selected, with detailed descriptive captions, including pertinent clinical data. The material is arranged anatomically, covering the thorax and contents, abdomen, skull and skeletal system. Each of these sections consists first of roentgenograms of the normal, the more common normal variants and the major pathologic variations, recognizable roentgenographically. Line drawings emphasizing the abnormal changes are frequent.

Illustrations of the more specialized examinations — angiography, encephalography, tonography and so forth — are limited to the normal and a few of the most typical pathologic variations. Very little space is given to the newborn and neonatal periods.

The book as an anthology of pediatric films is rewarding to study. It is well compiled and accurate.

The reproductions of the x-ray films are direct positive prints from negatives, with a resulting reversal of density values that may handicap those unaccustomed to transposing densities for actual x-ray-film reading. The superb engraving, rarely seen in medical books published in this country, yields a definition that greatly offsets the disadvantage of the reversed prints.

M. H. WITTENBORG, M.D.

Blood Supply and Anatomy of the Upper Abdominal Organs: With a descriptive atlas. By Nicholas A. Michels, M.A., D.Sc. (Louvain). 4°, cloth, 581 pp., with 172 illustrations, including 166 in color. Philadelphia: J. B. Lippincott Company, 1955. $24.00.

In the preface to this book, the author writes, "Experienced and successful surgeons realize that with a wide, basic knowledge of anatomy and embryology, both normal and aberrant, they are never at a loss when operating; that the best way to avoid exsanguinating hemorrhage and to prevent ischemia, gangrene and postoperative disconcerting bleeding is to know the blood vessels and how to manipulate and ligate them properly." The text gives full support to this basic concept. A splendid account is given of the embryology, topographic relations and developmental anomalies of the gastrointestinal tract and its outgrowths. Then follow chapters of the normal and varying blood supply of the liver, biliary apparatus, spleen, pancreas, duodenum, stomach, esophagus, great omentum, transverse mesocolon and small and large intestines. There are excellent chapters on the routes of the collateral circulation in the upper abdominal organs and the collateral arterial pathways to the liver after ligation of the hepatic artery and removal of the celiac axis. There is a very useful bibliography. A most informative descriptive atlas of variations is included at the end of the book and is based on the author's statistically analyzed dissections. This book is a most worthy addition to a surgeon's library.

BENJAMIN SPECTOR, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

A Modern Pilgrim's Progress for Diabetics. By Garfield G. Duncan, M.D., clinical professor of medicine, Jefferson Medical College, and director of the medical divisions of the Pennsylvania Hospital and the Benjamin Franklin Clinic, Philadelphia. 16°, cloth, 222 pp., with illustrations. Philadelphia: W. B. Saunders Company, 1956. $2.50.

Advances in Internal Medicine. Vol. 8. Edited by William Dock, M.D., State University of New York College of Medicine, New York City; and I. Snapper, M.D., Beth-El Hospital, Brooklyn. 8°, cloth, 366 pp., with illustrations, tables and plates. Chicago: The Year Book Publishers, Incorporated, 1956. $9.00.

Patterns of Mothering: Maternal influence during infancy. By Sylvia Brody, Ph.D. With an introduction by René A. Spitz, M.D. 8°, cloth, 446 pp., with 28 tables and 5 diagrams. New York: International Universities Press, Incorporated, 1956. $7.50.

The Recovery Room: Immediate postoperative management. By Max S. Sadove, M.D., professor of surgery (anesthesiology) and head, Division of Anesthesiology, University of Illinois College of Medicine and Research and Educational Hospitals; and James H. Cross, M.D., clinical assistant professor in surgery, University of Illinois College of Medicine. 8°, cloth, 597 pp., with illustrations. Philadelphia: W. B. Saunders Company, 1956. $12.00.

Treatment of Heart Disease: A clinical physiologic approach. By Harry Gross, M.D., attending physician, Montefiore Hospital, and assistant clinical professor of medicine, Columbia University College of Physicians and Surgeons; and Abraham Jezer, M.D., attending physician, Montefiore Hospital, and assistant clinical professor of medicine, Columbia University College of Physicians and Surgeons. 4°, cloth, 549 pp., with 91 illustrations. Philadelphia: W. B. Saunders Company, 1956. $13.00.

Composting: Sanitary disposal and reclamation of organic wastes. By Harold B. Gotaas, professor of sanitary engineering, Department of Engineering, University of California, Berkeley. 8°, paper, 205 pp., with 49 illustrations and 10 tables. Geneva: World Health Organization, 1956. £1. 5s., Sw. fr. 15.-, $5.00, for cloth-bound edition. (*World Health Organization, Monograph Series,* No. 31.) (Distributed in the United States by Columbia University Press, New York City.)

Malaria Conference for the Western Pacific and South-East Asia Regions: (Second Asian malaria conference). Baguio, Philippines, 15-24 November, 1954. 8°, paper, 44 pp., with 2 tables. Geneva: World Health Organization, 1956. 1/9, Sw. fr. 1.-, $0.30. Available also in French and Spanish editions. (*World Health Organization, Technical Report Series,* No. 103.) (Distributed in the United States by Columbia University Press, New York City.)

Food Hygiene: Fourth report of the expert committee on environmental sanitation. 8°, paper, 28 pp. Geneva: World Health Organization, 1956. 1/9, Sw. fr. 1.-, $0.30. Available also in French and Spanish editions. (*World Health Organization, Technical Report Series,* No. 104.) (Distributed in the United States by Columbia University Press, New York City.)

Expert Committee on Trachoma. Second report. 8°, paper, 20 pp. Geneva: World Health Organization, 1956. 1/9, Sw. fr. 1.-, $0.30. Available also in French and Spanish editions. (*World Health Organization, Technical Report Series,* No. 106.) (Distributed in the United States by Columbia University Press, New York City.)

Expert Committee on Professional and Technical Education of Medical and Auxiliary Personnel. Third report. 8°, paper, 20 pp. Geneva: World Health Organization, 1956. 1/9, Sw. fr. 1.-, $0.30. Available also in French and Spanish editions. (*World Health Organization, Technical Report Series,* No. 109.) (Distributed in the United States by Columbia University Press, New York City.)

Neue Beiträge zur Klinik und Pathogenese der Migräne. By Dr. Hartwig Heyck, neurosurgeon, Universitätspoliklinik, Kantonspital, Zürich. With a foreword by Prof. Dr. H. Krayenbühl. 4°, paper, 84 pp., with 16 illustrations. Stuttgart: Georg Thieme, 1956. DM 9.60.-, $2.30. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Atlas of Exfoliative Cytology. Supplement 1. By George N. Papanicolaou, M.D., Ph.D. 4°, paper, 86 pp., with 16 colored plates. Cambridge: Harvard University Press, 1956. $4.00. (Published for the Commonwealth Fund by the Harvard University Press.)

Annual Epidemiological and Vital Statistics, 1953. 4°, paper, 572 pp., with 74 tables. Geneva: World Health Organization, 1956. £2 10s., Sw. fr. 30.-, $10.00. Bilingual edition (French and English). (Distributed in the United States by Columbia University Press, New York City.)

The Neurosurgical Alleviation of Parkinsonism. By Irving S. Cooper, M.D., Ph.D., director, Department of Neurosurgery, St. Barnabas Hospital, assistant professor of neurologic surgery, New York University, Bellevue Medical Center, associate attending neurosurgeon, Bellevue Hospital, and associate attending neurosurgeon, University Hospital, New York City. 4°, cloth, 104 pp., with 68 illustrations. Springfield, Illinois: Charles C Thomas, 1956. $8.50.

Die Pathologie des kindlichen Pankreas. By Doz. Dr. med. Gerhard Seifert, assistant professor of pathology, Universitäts-Institut, Leipzig. 4°, cloth, 151 pp., with 109 illustrations and 15 tables. Leipzig: Georg Thieme, 1956. DM 52.- $12.00. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Treatment of Migraine. By John R. Graham, M.D., chief, Medical Service, Faulkner Hospital, Boston, clinical associate in medicine, Massachusetts General Hospital, and instructor in medicine, Harvard Medical School. 12°, cloth, 149 pp., with 8 illustrations. Boston: Little, Brown and Company, 1956. $4.00. (*New England Journal of Medicine,* Medical Progress Series.)

Health for the American People: A symposium, presented Monday, November 21, 1955 at the Massachusetts Memorial Hospitals centennial celebration. 12°, paper, 105 pp., with 1 illustration and 5 tables. Boston: Little, Brown and Company, 1956. $1.00.

A History of the Therapy of Tuberculosis and the Case of Frederic Chopin. By Esmond R. Long, M.D., director of the Henry Phipps Institute, University of Pennsylvania, and director of medical research, National Tuberculosis Association. 8°, cloth, 71 pp. Lawrence, Kansas: University of Kansas Press, 1956. $2.00. *(Logan Clendening Lectures on the History and Philosophy of Medicine,* sixth series.)

Ciba Foundation Symposium on Extrasensory Perception. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch.; and Elaine C. P. Millar, A.H.W.C., A.R.I.C. 8°, cloth, 240 pp., with 3 illustrations. Boston: Little, Brown and Company, 1956. $6.00.

Human Ovulation and Fertility. By Edmond J. Farris, Ph.D., executive director, associate member, Wistar Institute of Anatomy and Biology. 8°, cloth, 159 pp., with 35 illustrations, 56 tables and 3 colored plates. Philadelphia: J. B. Lippincott, 1956. $6.50.

Oral Cancer and Tumors of the Jaws. By George S. Sharp, M.D., professor of pathology, School of Dentistry, and assistant clinical professor of surgery, School of Medicine, University of Southern California, and director, Pasadena Tumor Institute; Weldon K. Bullock, M.D., M.Sc. (Path.), associate clinical professor of pathology, School of Medicine, University of Southern California, and surgical pathologist, Los Angeles County Hospital; and John W. Hazlet, D.D.S., lecturer on oral-tumor pathology, School of Dentistry, University of Southern California. 8°, cloth, 561 pp., with 25 illustrations and 2 tables. New York: The Blakiston Division, McGraw-Hill Book Company, Incorporated, 1956. $15.00.

Clinical Hematology. By Maxwell M. Wintrobe, M.D., Ph.D., professor of medicine and head, Department of Medicine, and director, Laboratory for the Study of Hereditary and Metabolic Disorders, University of Utah College of Medicine. Fourth edition. 8°, cloth, 1184 pp., with 236 illustrations, 62 tables and 20 plates. Philadelphia: Lea and Febiger, 1956. $15.00.

A Text Book of Pathology. By E. T. Bell, M.D. With contributions by B. J. Clawson, M.D., and J. S. McCartney, M.D., professor of pathology, University of Minnesota Medical School. Eighth edition. 8°, cloth, 1028 pp., with 545 illustrations and 5 colored plates. Philadelphia: Lea and Febiger, 1956. $14.50.

Physical Diagnosis. By Ralph H. Major, M.D., professor of medicine and history of medicine, University of Kansas School of Medicine; and Mahlon H. Delp, M.D., professor of medicine, University of Kansas School of Medicine. Fifth edition. 4°, cloth, 358 pp., with 536 illustrations. Philadelphia: W. B. Saunders Company, 1956. $7.00.

Cardiac Pressures and Pulses: A manual of right and left heart catheterization. By Aldo A. Luisada, M.D., associate professor of medicine, Chicago Medical School, director, Division of Cardiology, Chicago Medical School and Mount Sinai Hospital, and cardiologist, La Rabida Jackson Park Sanatorium; and Chi Kong Liu, M.D., instructor in medicine, Chicago Medical School, and chief, Laboratory of Catheterization of the Division of Cardiology, Chicago Medical School and Mount Sinai Hospital. 8°, cloth, 116 pp., with 51 illustrations and 5 tables. New York: Grune and Stratton, Incorporated, 1956. $6.00.

The Morphology of Human Blood Cells. By L. W. Diggs, M.D., professor of medicine and director of Medical Laboratories, University of Tennessee College of Medicine and City of Memphis Hospitals, and consultant in hematology, Armed Forces Institute of Pathology, Washington, D. C.; Dorothy Sturm, instructor, Memphis Academy of Arts; and Ann Bell, B.A., instructor in medicine, University of Tennessee College of Medicine. 4°, cloth, 181 pp., with 54 illustrations, 11 tables and 31 colored plates. Philadelphia: W. B. Saunders Company, 1956. $12.00.

Endogenous Uveitis. By Alan C. Woods, M.D. 4°, cloth, 303 pp., with 81 illustrations by Annette Smith Burgess, instructor in art as applied to medicine, Johns Hopkins University School of Medicine, 8 tables and 42 colored plates. Baltimore: The Williams and Wilkins Company, 1956. $12.50.

Clinical Orthopaedics. No. 7. Edited by Anthony R. DePalma, M.D., et al. 4°, cloth, 354 pp., with illustrations and tables. Philadelphia: J. B. Lippincott Company, 1956. $7.50.

Peaceful Uses of Atomic Energy: Proceedings of the International Conference in Geneva, August 1955: Vol. 10, Radioactive isotopes and nuclear radiations in medicine. 4°, cloth, 547 pp., with illustrations, tables and charts. New York: United Nations, 1956. $8.00. (Distributed in the United States by Columbia University Press, New York City.)

Peaceful Uses of Atomic Energy: Proceedings of the International Conference in Geneva, August 1955: Vol. 11, Biological effects of radiation. 4°, cloth, 406 pp., with illustrations, tables and charts. New York: United Nations, 1956. $8.00. (Distributed in the United States by Columbia University Press, New York City.)

A Doctor's Marital Guide for Patients: Written for those married or about to be married. By Bernard R. Greenblat, M.D., associate attending in obstetrics and gynecology, Kings County Hospital, Brooklyn, clinical instructor in obstetrics and gynecology, State University of New York, School of Medicine, Brooklyn, associate attending in gynecology, Hillside Hospital, Queens, New York, staff member in obstetrics and gynecology, Long Island Jewish Hospital, New Hyde Park, and assistant attending in obstetrics and gynecology, North Shore Hospital, Manhasset, New York. 16°, paper, 88 pp., with 12 illustrations. Chicago: The Budlong Press, 1956. $1.50. (Catholic edition also available.)

Plastic Repair of Genito-Urinary Defects. By George Bankoff, M.D., D.Ch., F.R.C.S.Ed., F.R.F.P.S., plastic surgeon, Gallinger Municipal Hospital, Washington, D.C., assistant surgeon, University Hospital, Bonn, and chief surgeon, Plastic Department, George Eastman Institute, Rome. 8°, cloth, 355 pp., with 86 illustrations. New York: Philosophical Library, 1956. $17.50.

A New Psychotherapy in Schizophrenia: Relief of frustrations by symbolic realization. By Marguerite Sechehaye. Translated by Grace Rubin-Rabson, Ph.D. 8°, cloth, 199 pp. New York: Grune and Stratton, 1956. $4.50.

Progress in Psychotherapy 1956. Edited by Frieda Fromm-Reichmann, M.D., Chestnut Lodge, Rockville, Maryland, and Center for Advanced Study in the Behavioral Sciences, Stanford, California; and J. L. Moreno, M.D., Moreno Sanitarium, Beacon, New York, and New York University, New York City. 8°, cloth, 352 pp. New York: Grune and Stratton, 1956. $8.50.

Röntgendiagnostik des Hüftgelenks. By Prof. Dr. med. R. Glauner, chief physician, X-Ray and Radium Section, Marienhospital, Stuttgart; and Doz. Dr. med. habil. W. Marquardt, chief physician, Orthopedic Clinic, "Paulinenhilfe," Stuttgart. 4°, cloth, 168 pp., with 195 illustrations and 1 table. Stuttgart: Georg Thieme, 1956. DM 51.30-. $13.60. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Synopsis of Gynecology: Based on the textbook Diseases of Women. By Robert James Crossen, M.D., associate professor of clinical gynecology and obstetrics, Washington University School of Medicine, associate gynecologist and obstetrician, Barnes Hospital and St. Louis Maternity Hospital, gynecologist, St. Luke's Hospital, and head, Unit 1 (Washington University), Obstetric and Gynecologic Service, St. Louis City Hospital. Fourth edition. 12°, cloth, 255 pp., with 131 illustrations, 1 table and a frontispiece. St. Louis: C. V. Mosby Company, 1956. $5.25.

Ciba Foundation Symposium jointly with the Physiological Society and the British Pharmacological Society on Histamine. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch.; and Cecilia M. O'Connor, B.Sc. 8°, cloth, 472 pp., with illustrations, tables, charts and a frontispiece. Boston: Little, Brown and Company, 1956. $9.00.

Meditations on Medicine and Medical Education: Past and present. By I. Snapper, M.D. 8°, cloth, 138 pp. New York: Grune and Stratton, 1956. $3.75.

Psychosomatic Aspects of Surgery. Edited by Alfred J. Cantor, M.D., consulting proctologist, Jersey City Medical Center, director of research in proctology, Intestinal Research Institute, Flushing, Long Island, permanent secretary, International Academy of Proctology, and editor-in-chief, *American Journal of Proctology;* and Arthur N. Foxe, M.D. 8°, cloth, 220 pp., with 1 illustration and 9 tables. New York: Grune and Stratton, 1956. $6.50.

Electrodiagnosis and Electromyography: Some clinical applications of electroneurophysiology. Edited by Sidney Licht, M.D. 8°, cloth, 272 pp., with 90 illustrations and 1 table. New Haven: Elizabeth Licht, 1956. $10.00.

Mental Health Planning for Social Action. By George S. Stevenson, M.D., Sc.D., national and international consultant, National Association for Mental Health, Incorporated, and consultant, United States Public Health Service, Department of Health, Education and Welfare, National Institute of Mental Health, and Veterans Administration. 8°, cloth, 358 pp. New York: The Blakiston Division, McGraw-Hill Book Company, Incorporated, 1956. $6.50.

Expert Committee on Drugs Liable to Produce Addiction. Sixth report. 8°, paper, 24 pp. Geneva: World Health Organization, 1956. Sw. fr. 1, 1/9, $0.30. (No. 102, *World Health Organization Technical Report Series.*) Published in French and Spanish also. (Distributed in the United States by Columbia University Press, New York City.)

Borderlands of the Normal and Early Pathologic in Skeletal Roentgenology. By Dozent Dr. E. A. Zimmer, Bern/Fribourg. English translation arranged and edited by James T. Case, M.D., D.M.R.E.(Cambridge), director, Memorial Cancer Foundation, Santa Barbara, California. Tenth edition, completely revised. 4°, cloth, 723 pp., with 1282 illustrations. New York: Grune and Stratton, Incorporated, 1956. $24.50.

Cytology of the Blood and Blood-Forming Organs. By Marcel Bessis, director, Research Laboratory, Centre National de Transfusion Sanguine, Paris, France. Translated by Eric Ponder, Nassau Hospital, Mineola, New York. 4°, cloth, 629 pp., with 405 illustrations and 22 colored plates. New York: Grune and Stratton, 1956. $22.50.

Virus Diseases and the Cardiovascular System: A survey. By Ernest Lyon, M.D. 8°, cloth, 215 pp. New York: Grune and Stratton, 1956. $5.75.

Progress in Hematology. Edited by Leandro M. Tocantins, M.D. With 27 contributors. 4°, cloth, 336 pp., with illustrations and tables. New York: Grune and Stratton, 1956. $9.75.

Anesthesia for Obstetrics: Labor, delivery, infant care. By Robert A. Hingson, M.D., professor of anesthesia, Western Reserve University School of Medicine, and director of anesthesia, University Hospitals of Cleveland; and Louis M. Hellman, M.D., professor of obstetrics and gynecology, State University of New York, College of Medicine at New York, and director of obstetrics and gynecology, King's County Hospital. 4°, cloth, 344 pp., with 122 illustrations and 71 tables. Philadelphia: J. B. Lippincott Company, 1956. $12.50.

Adrenal Function in Infants and Children: A symposium. Edited by Lytt I. Gardner, M.D., associate professor, Department of Pediatrics, State University of New York, College of Medicine, Syracuse, New York. 8°, cloth, 221 pp., with illustrations, tables and charts. New York: Grune and Stratton, 1956. $6.75.

Harnableitung in den Darm: Uretero-Sigmoidostomie und Darm-Ersatzblasenbildung. By Prof. Dr. H. Boeminghaus, Düsseldorf, Klinik Golzheim. 8°, paper, 59 pp., with 57 illustrations. Stuttgart: Georg Thieme, 1956. DM 15.- $3.60. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Der Fersenschmerz: Funktionelle und organische Störungen im Bereich der Ferse und Achillessehne. By Prof. Dr. med. Kurt Stucke, chief surgeon, Univ.-Klinik Würzburg. With a foreword by Prof. Dr. med. Werner Wachsmuth, director of surgery, Univ.-Klinik Würzburg. 8°, cloth, 163 pp., with 68 illustrations. Stuttgart: Georg Thieme, 1956. DM 29.70.- $7.10. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Behandlung innerer Krankheiten: Richtlinien und Ratschläge für Studierende und Ärzte. By Prof. Dr. Ferdinand Hoff, director, I. Medizinischen Universitätskinik, Frankfurt A. M. Seventh edition. 8°, cloth, 653 pp. Stuttgart: Georg Thieme, 1956. DM 57.- $13.60. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

The Practice of Medicine. Edited by John S. Richardson, M.V.O., M.A., M.D. (Cantab.), F.R.C.P., physician, St. Thomas's Hospital, London. 8°, cloth, 1076 pp., with 86 illustrations and 10 tables. London: J. and A. Churchill, Limited, 1956. $8.50. (Distributed in the United States by Little, Brown and Company, Boston.)

Poliomyelitis. By W. Ritchie Russell, C.B.E., M.D.(Edin.), D.Sc.(Oxon.), F.R.C.P.(Edin.), F.R.C.P.(Lond.), director, Department of Neurology, United Oxford Hospitals, clinical

lecturer in neurology, University of Oxford, and consultant neurologist to the Army. Second edition. 8°, cloth, 147 pp., with 40 illustrations and 5 tables. London: Edward Arnold (Publishers), Limited, 1956. $3.00. (Distributed in the United States by the Williams and Wilkins Company, Baltimore.)

Diseases of the Nose, Throat and Ear: A handbook for students and practitioners. By I. Simson Hall, M.B., Ch.B., F.R.C.P.E., F.R.C.S.E., surgeon to the Royal Infirmary, Edinburgh (Department for Diseases of Nose, Throat and Ear), and lecturer in diseases of nose, throat and ear, University of Edinburgh. Sixth edition. 12°, cloth, 463 pp., with 84 illustrations and 8 colored plates. London: E. and S. Livingstone, Limited, 1956. $4.75. (Distributed in the United States by the Williams and Wilkins Company, Baltimore.)

Tuberculosis in Obstetrics and Gynecology. By George Schaefer, M.D., F.A.C.S., F.I.C.S., assistant professor of clinical obstetrics and gynecology, Cornell University Medical College, and attending obstetrician and gynecologist, Triboro Hospital. 8°, cloth, 307 pp., with 54 illustrations and 22 tables. Boston: Little, Brown and Company, 1956. $8.75.

The Office Assistant: In medical or dental practice. By Portia M. Frederick, instructor, Medical Office Assisting, Long Beach City College; and Carol Towner, executive assistant, Department of Public Relations, American Medical Association. 8°, cloth, 351 pp., with 55 illustrations. Philadelphia: W. B. Saunders Company, 1956. $4.75.

The Management of Menstrual Disorders. By C. Frederic Fluhmann, M.D., C.M., clinical professor of obstetrics and gynecology, Stanford University School of Medicine, San Francisco, and assisting visiting obstetrician and gynecologist, Stanford-Lane Hospitals. 8°, cloth, 350 pp., with 121 illustrations and 4 tables. Philadelphia: W. B. Saunders Company, 1956. $8.50.

NOTICES

MASSACHUSETTS ACADEMY OF GENERAL PRACTICE

The Fall Clinical Assembly of the Massachusetts Academy of General Practice will be held at the Hotel Statler, Boston, on Wednesday, September 26. Both morning and afternoon sessions will be held in the Grand Ballroom.

PROGRAM

9:00 a.m. Welcome. Dr. William H. Chasen, president. Films. Congenital Malformation of Heart.

10:00 a.m. Drugs Used in Treatment of Hypertension. Dr. Dale G. Friend, associate in medicine, Harvard Medical School, and senior associate in medicine, Peter Bent Brigham Hospital.

10:30 a.m. Coffee Break and Visits to Exhibits.

11:00 a.m. Some Less Common Types of Renal Disease. Dr. Joseph M. Hayman, Jr., Dean, Tufts University School of Medicine.

11:30 a.m. The Neuroanatomic Background Underlying Dizziness and Vertigo. Dr. Benjamin Spector, professor of bio-anatomy, chairman, Department of Anatomy, and professor of the history of medicine, Tufts University School of medicine.

12:00 m. Recess and Visits to Exhibits.

12:30 p.m. Luncheon.

2:00 p.m. Gynecology for the General Practitioner. Dr. Christopher J. Duncan, associate chief surgeon, Free Hospital, Brookline, associate in obstetrics, Massachusetts General Hospital, and clinical associate in gynecology, Harvard Medical School.

2:30 p.m. The Useless Applications of Chemotherapeutic Agents. Dr. Louis Weinstein, associate professor of medicine, Boston University School of Medicine, lecturer on infectious disease, Harvard Medical School, and chief, Department of Infectious Diseases, Massachusetts Memorial Hospitals.

3:00 p.m. Coffee Break and Visits to Exhibits.

3:30 p.m. Unusual Rheumatic Diseases. Dr. Theodore B. Bayles (moderator), director of research and visiting physician, Robert Breck Brigham Hospital, associate in medicine and chief of the arthritis clinic, Peter Bent Brigham Hospital, and clinical associate in medicine, Harvard Medical School; Dr. Theodore A. Potter, lecturer in orthopedic surgery, Tufts University School of Medicine; Dr. Charles L. Short, associate physician, Massachusetts General Hospital, instructor in medicine, Harvard Medical School, and consultant, Mount Auburn Hospital, Cambridge; Dr. James S. Stillman, junior physician, Boston City Hospital, chief of medical services, Robert Breck Brigham Hospital, instructor in medicine, Harvard Medical School, and lecturer in medicine, Boston University School of Medicine; and Dr. John G. Kuhns, chief, orthopedic staff, Robert Breck Brigham Hospital, attending orthopedic surgeon, Children's Hospital, and consultant in orthopedic surgery, Sturdy Memorial Hospital, Attleboro.

5:30 p.m. Cocktail Reception.

7:00 p.m. Dinner. The speaker will be Major General William E. Shambora, commanding general, Brooke Army Medical Center, Fort Sam Houston, Texas. Major General Shambora will talk on the subject "The Objectives and Activities of the Brooke Army Medical Center."

AMERICAN COLLEGE OF GASTROENTEROLOGY

The annual convention of the American College of Gastroenterology will be held at the Roosevelt, New York City, October 15-17. The program will include panel discussions on diseases of the gastrointestinal tract, one to be presented by each of the six medical schools in New York City. The sessions will be open to all physicians.

The annual course in postgraduate gastroenterology will be under the direction of Drs. Owen H. Wangensteen, Minneapolis, Minnesota, and I. Snapper, Brooklyn, New York. The course will be given at the Roosevelt and the new Metropolitan Hospital Center, October 18 through 20. All physicians who have registered in advance may participate.

Further information may be obtained from the American College of Gastroenterology, 33 West 60th Street, New York 23, New York.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 13–27. Consultation Clinics for Crippled Children in Massachusetts. Page 446, issue of August 30.

SEPTEMBER 18. South End Medical Club. Page 402, issue of August 23.

SEPTEMBER 19. Overholt Thoracic Clinic. Page 489, issue of September 6.

SEPTEMBER 19 and 20. San Diego Postgraduate Assembly. Page 360, issue of August 16.

SEPTEMBER 19 and 26 and OCTOBER 3 and 10. Lahey Clinic Fellowship Lectures. Page 489, issue of September 6.

SEPTEMBER 26. Massachusetts Academy of General Practice. Notice above.

SEPTEMBER 27–29. University of Michigan Medical School. Page 402, issue of August 23.

SEPTEMBER 28 and 29. Mississippi Valley Medical Society and American Medical Writers' Association. Page 402, issue of August 23.

OCTOBER 4, 5 and 6. Academy of Psychosomatic Medicine. Page 402, issue of August 23.

OCTOBER 5 and 6. New England Surgical Society. Page 489, issue of September 6.

OCTOBER 7, 8 and 9. New Hampshire and Vermont State Medical Societies. Page 304, issue of August 9.
OCTOBER 8–12. American Society of Anesthesiologists. Page 490, issue of September 6.
OCTOBER 8–13. International Cancer Cytology Congress. Page 104, issue of July 12.
OCTOBER 9–13. American Rhinologic Society. Page 490, issue of September 6.
OCTOBER 12. New England Rheumatism Society. Page 489, issue of September 6.
OCTOBER 15–17. American College of Gastroenterology. Page 539.
OCTOBER 15–26. New York Academy of Medicine. Page 304, issue of August 9.
OCTOBER 19 and DECEMBER 14, 1956, and FEBRUARY and APRIL, 1957. Massachusetts Society for Research in Psychiatry. Page 56, issue of July 5.
OCTOBER 30 and 31 and NOVEMBER 1. New England Postgraduate Assembly, Boston.
NOVEMBER 12–16. American Public Health Association. Page 402, issue of August 23.
NOVEMBER 14–22. Pan-Pacific Surgical Association. Page 490, issue of September 6.
NOVEMBER 18–22. Pan American Medical Association. Page 490, issue of September 6.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 20

THURSDAY, SEPTEMBER 20

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Yamins A, Beth Israel Hospital.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. Surgery for Esophageal Lesions. Drs. Dwight E. Harken and Harrison Black. Main Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, SEPTEMBER 21

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Medical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*12:30–1:30 p.m. Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, SEPTEMBER 22

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*9:00–10:00 a.m. Anesthesiology Conference. Dr. Benjamin Etsten. Anesthesia Laboratory, New England Center Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, SEPTEMBER 24

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Endocrine Conference. Dr. Astwood. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. X-Ray Conference. Dr. William Carey. Saint Elizabeth's Hospital.
*3:00–4:00 p.m. Neuroradiologic Conference. Dr. Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Surgical Conference Room, Peter Bent Brigham Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Dr. Benjamin Etsten. Stearns Auditorium, New England Center Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. Edward T. MacMahon. Stearns Auditorium, New England Center Hospital.

TUESDAY, SEPTEMBER 25

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical Grand Rounds. Pathology Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Medical Grand Rounds. Main Conference Room (Ground Floor), Lemuel Shattuck Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. (Cafeteria) New England Deaconess Hospital.
*2:00–3:00 p.m. Hematology Conference. Dr. Mario Stefanini. Saint Elizabeth's Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetric). Faulkner Hospital.

WEDNESDAY, SEPTEMBER 26

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. Deaconess II, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Auditorium, Carney Hospital, Dorchester.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery and Psychiatry Conference. Drs. John F. Sullivan, Justin Hope and Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Medical-Surgical Rounds. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*6:00 p.m. Lahey Clinic Fellowship Lecture. What the Physician Should Know About Hospitals. Dr. James E. Fish. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.